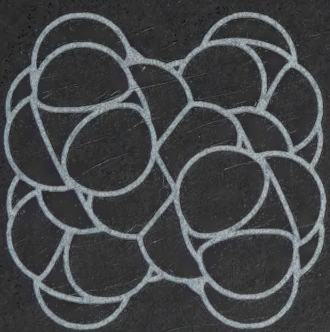
STERIC INTERACTIONS BETWEEN ALKYL AND PHENYL GROUPS IN AMIDES, ETHYLENES AND STYRENES

A dynamic NMR and molecular mechanics investigation

Ingrid Pettersson



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Title and subtitle STERIC INTERACTIONS BETWEEN ALKYL AND PHENYL GROUPS IN AMIDES, ETHYLENES AND STYRENES. A dynamic NMR and molecular mechanics investigation.

Abstract

The steric interactions between alkyl and phenyl groups have been studied.

Synthesis of some N-alkyl-2,6-dimethyl(thio)anilides, N,N-di-isopropyl(thio,seleno)benzamide, α,β-substituted styrenes and tetra-primary-alkylethylenes have been presented.

Conformations of the alkyl and aryl groups and free energy barriers to rotation have been studied by dynamic ^{1}H NMR and by molecular mechanics calculations.

In the amides and styrenes the alkyl groups interact essentially with the "face" of the phenyl ring and the effective steric size of the phenyl ring, based on the free energy differences between two conformations, was shown to depend, among other things, upon the geometrical relationship between the phenyl ring and the alkyl groups it interacts with.

One chiral α,β-substituted styrene have been resolved into stable enantiomers on microcrystalline triacetylcellulose.

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Signature Ingrid Pettersson Date October 4, 1984

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This review summarizes results from the following papers which will be referred to by the Roman numerals I-V.

I. I. Pettersson and J. Sandström
Conformational Analysis of Crowded Anilides and Thioanilides. The "En-Face" Steric Effect of Aryl Groups.
Acta Chem. Scand. B 38 (1984) 397.

II. I. Pettersson and U. Berg
Conformational Analysis of α-Alkyl-β,β-di-isopropylstyrenes. A Dynamic ^{1}H N.m.r. and Molecular Mechanics Investigation.
Manuscript.

III. I. Pettersson and U. Berg
Enantiomer Resolution, and Stereodynamic and Chiroptical Properties of β,β-Di-isopropyl-α,2-dimethylstyrene.
J. Chem. Res. (S) (1984) 208.

IV. U. Berg and I. Pettersson
Conformational Equilibria and Torsional Barriers of the Isopropyl Groups in N,N-Diisopropylbenzamide and its Thio and Seleno Analogues.
Manuscript.

V. L. Andersen, U. Berg and I. Pettersson
Static and Dynamic Stereochemistry of Tetra-primary-alkylethylenes.
J. Org. Chem. In press.

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1. INTRODUCTION

1.1 Background

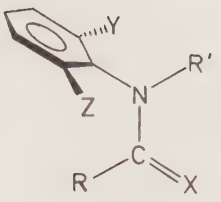
The effective steric size of a phenyl ring has been examined in several systems and it sometimes appears larger than a tert-Bu group and sometimes smaller than a methyl group,[1-7] as summarized in Table 1. This variation of the

Table 1. Selected Steric Parameters.

	H	CH_3	iPr	tBu	Ph	Ref
E_s	1.24	0.00	-0.47	-1.54	-2.55	1
I^{X-H}	ca. 4	40.4	52.6	76.6	33.1	2
A	0	1.70	2.15	4.2 [a]	3.0	3
P	0	2.1	—	3.1	1.9	4
υ	0	0.52	0.76	1.24	0.57	5
S^o	0	-0.73	-1.44	-3.94	-1.82	6
r	—	0	-1.5	-2.6	-0.58	7

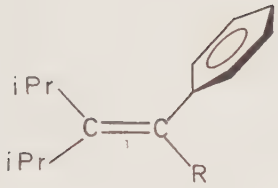
[a] Lower limit.

effective steric size depends among other factors on the conformation of the phenyl ring,[5c] since the effective size of such a ring is quite different laterally and "en face". In order to investigate the effective steric size of the "face" of the phenyl ring and its interactions with alkyl groups three different systems were designed (1-3), in which a phenyl ring is attached to a planar framework. In these systems, the phenyl ring is almost orthogonal to the sp^2-framework.



X = O, S

1



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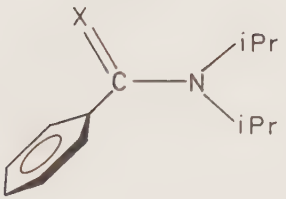


X = O, S, Se

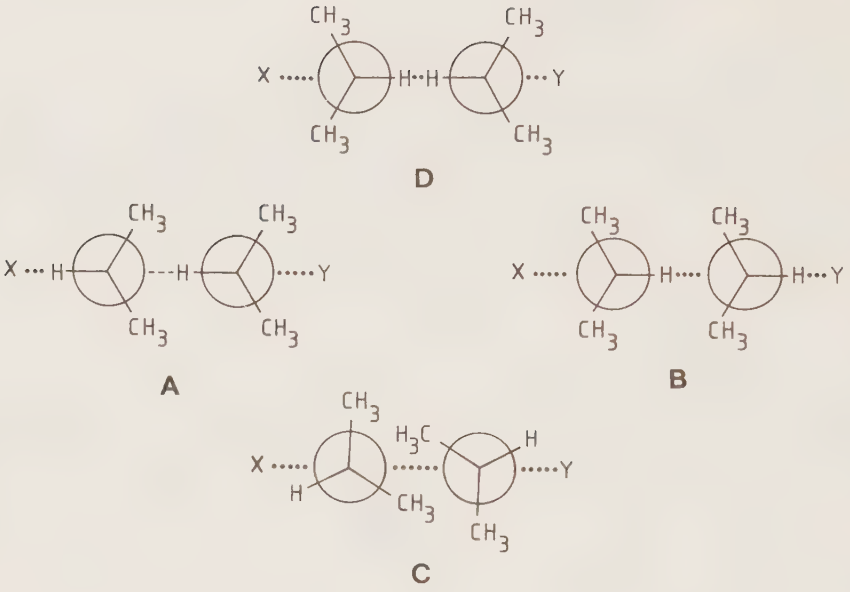
3

Dynamic ^{1}H NMR was used for the studies of the conformations and the barriers to conformational interchange. Molecular mechanics (MM) calculations[8,9] were carried out to aid in the assignment of the NMR signals to the observed conformations at low temperatures and to attempt to understand the mechanisms of the conformational interchange.

1.2 Interactions involving secondary alkyl groups and a phenyl ring attached to a planar framework

Two adjacent isopropyl groups attached to a planar framework have been found to exist in four general types of rotamers (A-D, Scheme 1), of which the two "gear-meshed" conformations A and B are in most cases lowest in energy.[10-18]

Conformation A is favoured by a large X combined with a small Y while the reverse holds for conformations of type B. Conformations of type C should be regarded as systems in equilibrium between two rapidly exchanging enantiomeric forms, and are favoured by large flanking groups, X and Y. By deter-

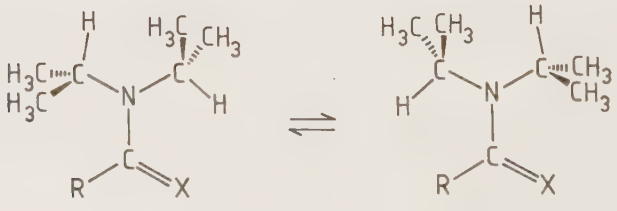


Scheme 1

mining the relative energies of A and B, the relative steric demands of the flanking groups, X and Y, can be estimated.

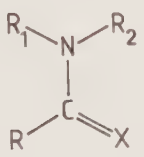
If X is a phenyl ring and Y is an alkyl group, the relative size of a phenyl ring can be estimated (Papers II and III; see Section 3.2).

N,N-Di-isopropylamides and -thioamides exist mainly as a mixture of two rotameric forms, 4A and 4B.[11-17] The equilibrium

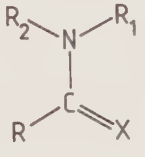


is displaced toward 4B by increasing the size of R or decreasing the size of X. If R = Ph and X = O, S, and Se, the size of a phenyl ring in comparison with X (X = O, S and Se) can be obtained (see Section 3.3). This is discussed in Paper IV.

By replacing the isopropyl groups in 4 with R^1 and R^2 and determine the equilibrium between 5A and 5B it is possible to obtain the relative sizes of R^1 and R^2. The largest of R and X



5 A



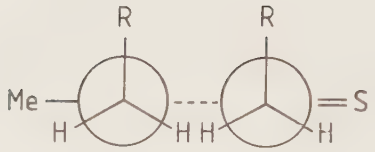
5 B

will be on the same side of the C(=X)-N bond as the smallest of R^1 and R^2. If R^1 or R^2 is a phenyl ring with methyl groups in the ortho positions it is possible to estimate the steric demand of the "face" of an aryl ring, since the ortho substituents cause the aryl group to be orthogonal to the amide plane (Paper I; see Section 3.1).

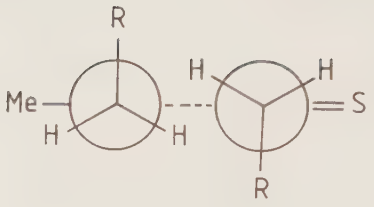
1.3 Interactions between primary alkyl groups attached to a planar framework

A primary alkyl group attached to a planar framework has a twofold rotational barrier with an approximately perpendicular conformation as the most stable one.[10] Two primary alkyl groups next to each other can be either parallel or antiparallel, and they are usually antiparallel.

The conformations and rotational barriers of the primary alkyl groups in N,N-dineopentylthioacetamide have been studied by dynamic ^{1}H NMR.[19] The antiparallel conformation, 6B, was shown to be the most stable one. The interconversion between the two enantiomeric antiparallel conformations 6B was shown to be a stepwise rotation of one alkyl group at a time. The



6A



6 B

barrier to rotation of the alkyl groups was too low to be measured if R = Me, Et, Ph. When R = iPr or tBu the barrier to rotation was determined to be 8.2 and 14.2 kcal mol^{-1}, respectively.

According to X-ray crystallography and MM calculations, hexaethylbenzene has the alkyl groups projecting alternately above and below the ring plane in the minimum energy conformation.[20]

In 1,3,5-trineopentylbenzenes, the rotamer with all three neopentyl groups projecting toward the same side of the benzene ring was shown by ^{1}H and ^{13}C NMR,[21] by MM calculations,[22] and by X-ray crystallography[23] to be the most stable one. This is indicated by the MM calculations to be due to a dominance of attractive nonbonded interactions among the alkyl groups.

In the present work a series of tetra-primary-alkylethylenes was prepared in order to study the conformations and barriers to rotation of the alkyl groups when four primary alkyl groups are attached to a double bond, (Paper V; see Section 4).

2. EXPERIMENTAL AND THEORETICAL METHODS

Dynamic ^{1}H NMR spectroscopy[24] has been the main experimental tool for the studies discussed in this thesis. At low temperatures, two (or in some cases three) different conformers of the same molecule were detected. The populations and rate constants were determined by computer simulation of the spectra. The ^{1}H NMR spectra discussed in Paper I were recorded on a JEOL Model MH 100 spectrometer, and those discussed in Papers II, III, IV, and V on a Nicolet 360 WB spectrometer. The free energy of activation, $\Delta G^{\ddagger}$, was calculated from the rate constants utilizing the Eyring equation (eq. 1). The free energy differences were determined from the populations (eq. 2). In this equation p_A is the fractional molar population of conformation A.

$$\Delta G^{\ddagger} = 4.575 \cdot 10^{-3}\ T \left[10.319 + \log \frac{T}{k} \right] \text{kcal mol}^{-1} \qquad (1)$$

$$\Delta G^{\circ} = 1.987 \cdot 10^{-3}\ T \ln \frac{p_A}{p_B} \text{ kcal mol}^{-1} \qquad (2)$$

UV and CD spectra were used in some cases (Papers II and III), and in one case, X-ray crystallographic analysis was carried out (Paper V).

Molecular mechanics calculations[8,9] were used to aid in the assignment of the conformations observed with ^{1}H NMR at low temperature, and to study possible pathways for conformational interconversion between them. In the MM method the steric energy is expressed as a sum of energy contributions:

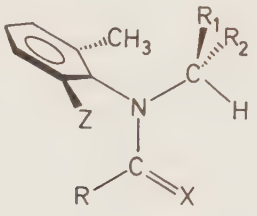
$$E_{steric} = E_{stretch} + E_{bend} + E_{torsion} + E_{vdW} + E_{dipole} + \text{cross terms}$$

The values of the energy contributions are calculated using empirically parametrized potential functions, and the total steric energy is obtained by energy minimization with respect to all internal degrees of freedom. The force fields developed by Allinger *et al.* (MMPI,[25-27] MM2,[9,28,29] MMP2[9,30]) were used.

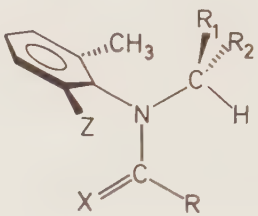
3. INTERACTIONS BETWEEN AN ALKYL GROUP AND A PHENYL RING

3.1 N-Alkyl-2,6-dimethylanilides

The conformation of geminal alkyl and aryl groups was studied in a series of anilides (7). R, R^1, R^2, X, and Z are



7 E



7 Z

defined in Table 2. In order to achieve a conformation in which the phenyl ring is perpendicular to the amide plane, the phenyl ring was substituted in the ortho positions. This causes interactions between the alkyl group and the "face" of the phenyl ring.

Three different kinds of rotational processes were investigated:

1) rotation around the RCX-N bond
2) rotation around the N-CHR^1R^2 bond
3) rotation around the N-Ar bond

The assignment of E and Z rotamers was based on the chemical shift of the R protons, with N,N-diisopropyl-[13] and N,N-dineopentyl- and isobutyl(thio)amides[19] as references. For the compounds, that exist in two rotameric forms, the assignment was verified by the aromatic solvent induced (ASIS)[31,32] method. The fractional populations of the E forms and the barriers to amide bond rotation are shown in Table 2. In all compounds except 16 the E form was shown to be the only or the major conformation. This is in accordance with results for N-benzyl-N-(o-tolyl)amides[33] and for N-methyl-acetanilide.[34] Since the phenyl ring prefers to be on the same side of the amide plane as the largest of R and C=O,[13] it can be concluded

Table 2. Substituents in compounds 8-18 (see structure 7), fractional populations of the E forms and $\Delta G^{\ddagger}$ for the E → Z exchange.

Comp.	X	Z	R	R^1	R^2	p_E [a]	$\Delta G^{\ddagger}_{E \rightarrow Z}$ [b]
8	O	CH_3	CH_3	H	$C(CH_3)_3$	1.00	–
9	S	CH_3	CH_3	H	$C(CH_3)_3$	1.00	–
10	O	CH_3	$C(CH_3)_3$	H	$C(CH_3)_3$	1.00	–
11	S	CH_3	$C(CH_3)_3$	H	$C(CH_3)_3$	0.84	20.8
12	O	Cl	$C(CH_3)_3$	H	$C(CH_3)_3$	1.00	–
13	O	Cl	$C(CH_3)_3$	H	$CH(CH_3)_2$	1.00	–
14	S	Cl	$C(CH_3)_3$	H	$CH(CH_3)_2$	0.69	21.4
15	O	CH_3	H	CH_3	CH_3	0.92	24.5
16	S	CH_3	H	CH_3	CH_3	0.44	24.8
17	O	CH_3	CH_3	CH_3	CH_3	1.00	–
18	S	CH_3	CH_3	CH_3	CH_3	1.00	–

[a] At +25 °C in o-dichlorobenzene. [b] Kcal mol^{-1}.

that the "face" of the phenyl ring is smaller than the methyl group or any other alkyl group in these systems.

The barrier to rotation of the CHR^1R^2 group was too low to be measured with dynamic NMR. Molecular mechanics calculations (MMPI) were performed on compound 9 and the E form was calculated to be 2.9 kcal mol^{-1} more stable than the Z form. The lowest energy minimum was found for a conformation with the benzene ring perpendicular to the thioamide plane and the neopentyl group symmetrically bisected by this plane (Figure 1). Rotation ca. ± 90° leads to a minimum only 0.2 kcal mol^{-1} above the lowest minimum. The barrier to rotation between them was calculated to be 3.1 kcal mol^{-1}.

Molecular mechanics calculations on compound 16 predicted

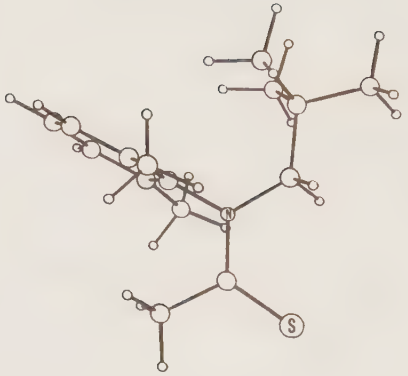


Figure 1. Minimum energy conformation of 9E.

the Z form to be more stable than the E form as experimentally found. As for compound 9 the phenyl ring is perpendicular to the amide plane and the C(=S)-N-C-H dihedral angle is 47°, with one of the methyl groups in the isopropyl group lying above the phenyl ring in the most stable conformation. The conformation, in which the C(=S)-N-C-H angle is 168° is only 0.45 kcal mol^{-1} less stable. In the E form the most stable conformation is when the phenyl ring is perpendicular to the thioamide plane and the C(=S)-N-C-H angle is 43° (Figure 2), with a second minimum, 1.2 kcal mol^{-1} higher, at 160°. The calculations predict that the exchange of the isopropyl group should not be observable by dynamic NMR. The barrier to isopropyl group rotation was calculated to be 3.9 kcal mol^{-1} in the E form.

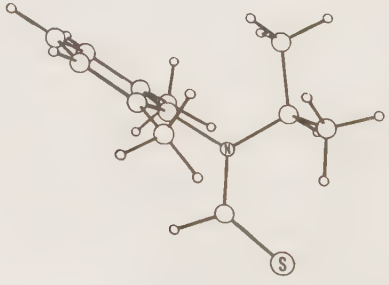
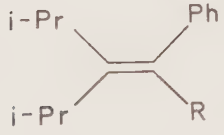


Figure 2. Minimum energy conformation of 16E.

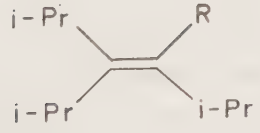
For symmetry reasons the rotation of the aromatic ring can only be observed if the benzene ring is unsymmetrically substituted (compounds 12, 13, and 14). The NMR spectra showed geminal nonequivalence for the methylene protons and the isopropyl methyl groups (13 and 14) at ambient temperature. No band broadening due to exchange was shown below +170 °C, which gives a lower limit to the free energy to rotation of 26 kcal mol^{-1}.

3.2 Interactions between an isopropyl group and a phenyl ring in substituted styrenes

In order to investigate the interactions between a phenyl ring and an isopropyl group in cis-vicinal position, a series of six different styrenes, substituted in the α- and β-positions was prepared (Scheme 3), and studied with respect to the conformations of the isopropyl groups and the barriers to conformational interconversion. Compounds 25 and 26 were studied for comparison.



R	
H	19
CH_3	20
C_2H_5	21
$(CH_3)_2CH$	22
$(CH_3)_3CH_2$	23
$(CH_3)_3C$	24



R	
H	25
CH_3	26

Scheme 3

The NMR spectra for 19 and 25 indicate the existence of only one conformation at low temperatures, while 20, 21, and 22 show a major conformation and a very small amount of a minor conformation. Compounds 23, 24, and 26 show somewhat more similar proportions of two conformations at low temperatures. Fractional populations and barriers to rotation are shown in Table 3. The assignment of the conformations is based on chemical shifts, double resonance and the NOE difference technique, as well as on the results of molecular mechanics calculations (MM2 and MMP2). Structures of all conformers of the styrenes that are observed in the NMR spectra at low temperatures, calculated by MMP2, are shown in Figure 3. In compounds 20-24 the phenyl ring is twisted ca. 70-90° out of the ethylene plane. In 19 the twist angle is reduced to 52°. The conformation, in which the cis-isopropyl group turns its methine hydrogen toward the phenyl ring is the major one for compounds 19-23 while the conformation in which the cis-isopropyl group turns its methyl groups toward the phenyl ring is the major one for compound 24. In all compounds the cis-isopropyl group interacts with the "face" of the phenyl ring. However, the isopropyl group shows a definite preference to turn its most bulky side, (the methyl groups) away from the phenyl ring.

Based on the free energy differences, the following order of relative effective size can be obtained

$$H << CH(CH_3)_2 < CH_3 \leq C_2H_5 < CH_2C(CH_3)_3 < Ph < C(CH_3)_3$$

Note that in compound 22, the isopropyl group geminal to the phenyl ring turns its methyl groups toward the phenyl ring. In addition to avoiding repulsive interaction with its cis-isopropyl group, this conformation is stabilized by the eclipsing of the double bond by the methine hydrogen.

In compounds 20-24 and 26 the exchange between two conformations is suggested to proceed through a stepwise rotation of the isopropyl groups in accordance with earlier findings.[10-13] This was illustrated with MM calculations for compound 26.

Table 3. Fractional populations, ΔG° (minor − major) and $\Delta G^{\ddagger}$ (major → minor) for compounds 19-26. The major and minor conformations (A, B, and C) are designed as in Figure 3.

Compound	Major conf., %		Minor conf.	ΔG° [a]	T [b]	$\Delta G^{\ddagger}$ [a]	T [b]
19	A	≥ 99	—	> 1.5	—	—	—
20	A	97-99.5	(B)	1.3-2.2	225	11.3	225
21	A	97-99.5	(B)	1.3-2.2	225	11.1	225
22	A	97-99.5	(B)	1.3-2.2	253	12.0	253
23	A	65	B	0.27 ± 0.05	218	11.5	240
24	B	91	C	0.75 ± 0.10	164	10.5	210
25	B	≥ 99	—	≥ 1.5	—	—	—
26	A	73	B	0.60 ± 0.10	203	12.2	234

[a] Kcal mol^{-1}. [b] K.

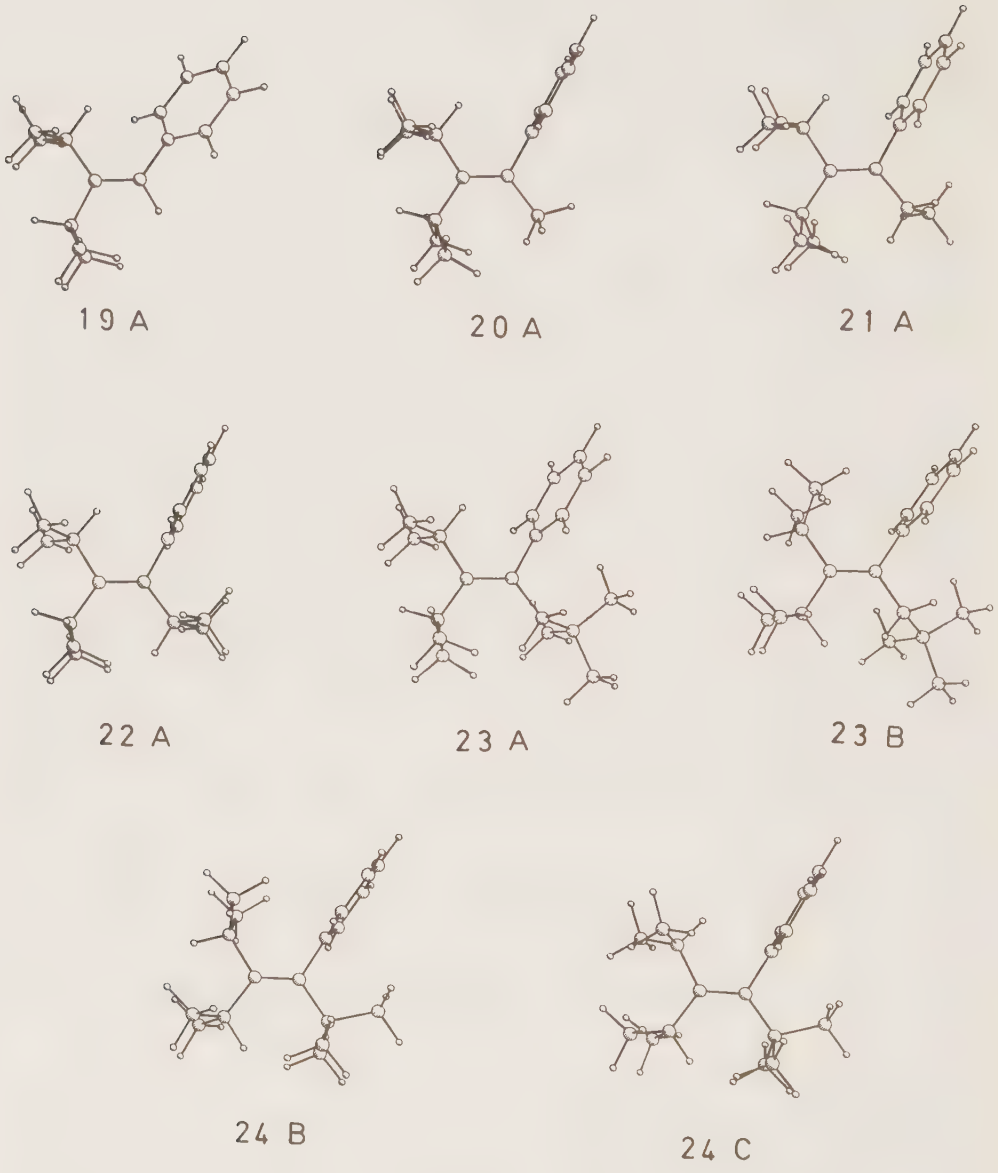


Figure 3. Structures of all conformers of compounds 19-24 that are appreciably populated as calculated by the MMP2 force field

If one of the ortho positions in the phenyl ring is substituted with e.g. a methyl group, the molecule becomes chiral. If the barrier to rotation of the aryl group is high enough, resolution of the compound into its enantiomers is possible. This was done for compound 20 (Paper III). Dynamic NMR gave $\Delta G^{\ddagger}_{465} = 26.8 \pm 0.3$ kcal mol^{-1} for the aryl group rotation. The compound was resolved into stable enantiomers on microcrystalline triacetylcellulose.[35,36] Thermal racemization in propanol at five different temperatures (50-70 °C) resulted in the following activation parameters for the rotational barrier of the aryl group: $\Delta G^{\ddagger}_{340} = 25.4 \pm 0.1$ kcal mol^{-1}, $\Delta H^{\ddagger} = 18.9 \pm 1.0$ kcal mol^{-1} and $\Delta S^{\ddagger} = -19 \pm 3.0$ cal mol^{-1} K^{-1}. The results from dynamic NMR and thermal racemization are compatible if the difference in temperatures is taken into account. Dynamic NMR at low temperatures gave results similar to those for the ortho unsubstituted compound 20, and the most stable conformation at low temperatures is the same as for 20. The dihedral angle between the phenyl ring and the double bond falls in the same range as for the other styrenes studied.

3.3 Interactions between an isopropyl group and a phenyl ring in N,N-di-isopropylbenzamide and its thio and seleno analogues

N,N-Di-isopropyl-(thio,seleno)benzamide is a system that is structurally related to the α,β-substituted styrenes discussed in Section 3.2. The conformations of the isopropyl groups in N,N-di-isopropylthiobenzamide have been studied with dynamic NMR at low temperatures by Ramey et al.[18] The authors observed two conformations at low temperatures, and suggest the major one to be of type C and the minor one of type B (X = Ph, Y = (=S); Scheme 1). N,N-Di-isopropylthiobenzamide was reinvestigated in the present thesis and the oxygen and seleno analogues were included. The results showed that the oxygen compound exists in one onformation only, and the thio and seleno analogues in three conformations at low temperatures.

The ^{1}H NMR spectra at ambient temperature indicate that the rotation around the amide bond is slow for the thio and seleno compounds, but still has some influence on the bandshape for the oxygen compound. Furthermore, the NMR spectra for the thio and seleno analogues showed one broadening at 0 °C and at ambient temperature, respectively, and another broadening at -75 °C and at -66 °C. The proposed conformations, based on comparisons with chemical shifts of other N,N-di-isopropylamides as references,[11-13] and fractional populations at low temperatures, are shown in Figure 4. Inserted values are chemical shifts at low temperature. The proposed conformations for the thio compound are not in agreement with earlier proposals by Ramey *et al.*[18] The barriers to isopropyl group rotation are shown in Table 4. In all three compounds conformation a is

Table 4. Free energy barriers to isopropyl group rotation in PhC(=X)-N(iPr)$_2$. The designations a, b, and c refer to Fig. 4.

X	Temp., K	$\Delta G^{\ddagger}_{a \rightarrow (b+c)}$ kcal mol^{-1}	Temp., K	$\Delta G^{\ddagger}_{c \rightarrow b}$ kcal mol^{-1}
S	269	13.2	198	9.3
Se	291	13.7	216	8.9

found to be the major one, and the effective size of the phenyl ring is larger than that of X (X = O, S, and Se) in these systems.

The fractional population of conformations (b + c) increases as the size of X increases. The increase in population of rotamer b relative to c on going from the thio to the selenoamide may be explained by a larger twist between the benzene and the amide planes in the seleno compound. This should diminish the interactions between the benzene ring and the E-isopropyl group in the b form, whereas no similar relative stabilization is expected for the c form.

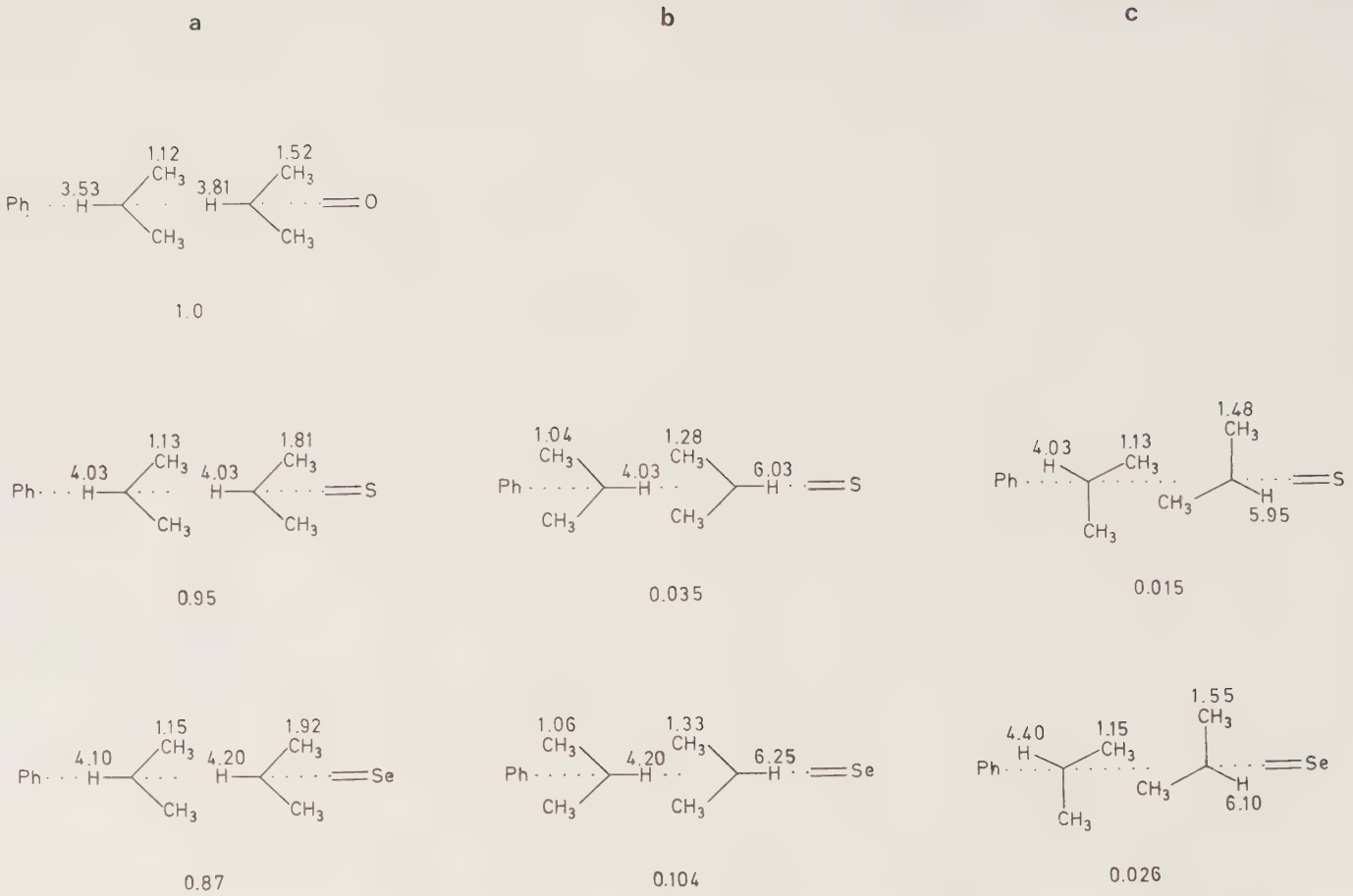


Figure 4. Chemical shifts and fractional populations of N,N-di-isopropyl-(thio,seleno)benzamide.

The dihedral angle between the amide plane and the phenyl ring in the crystal of N,N-dimethylthiobenzamide is 63°.[37] This angle is probably larger in the seleno compound, in view of the chemical shifts of the E-N-methyl protons.[38] Further increases could be expected if the N-methyl groups are replaced by N-isopropyl groups.

The high energy rotational process of the isopropyl group giving rise to band broadening and decoalescence around 0 °C for the thioamide and around ambient temperature for the selenoamide, is identified as the rotation of the Z-isopropyl group. This assignment is based on the large chemical shift difference ($\Delta\delta$ = 0.5) between the two isopropyl methyl doublets emerging at low temperature, induced by anisotropy of the C=X bond. This barrier shows a higher value when X = Se than when X = S. The barrier to rotation for the process with coalescence at -75 °C (X = S) and at -66 °C (X = Se) is ascribed to the rotation of the E-isopropyl group past the phenyl ring. This barrier has a lower value for the seleno compound than for the thio compound, which could be explained by an increased twist between the amide plane and the phenyl ring in the seleno than in the thio compound, as previously discussed.

The rate constant for the rotation of the E-isopropyl group is about five power of magnitude larger than the rate constant for rotation of the Z-isopropyl group ($\Delta S^{\ddagger}$ assumed zero). This and the fact that conformation c is observed with ^{1}H NMR at low temperature, shows that the process a $\rightleftharpoons$ b is stepwise, in accordance with earlier findings.[10-12]

4. INTERACTIONS BETWEEN PRIMARY ALKYL GROUPS. Tetraalkylethylenes

The stereochemistry of tetraethyl (27), tetrapropyl (28), tetraisobutyl (29), tetraneopentyl (30) and tetrabenzyl (31) ethylene has been investigated by dynamic ^{1}H NMR, X-ray analysis (for compound 31) and molecular mechanics calculations (MM2, MMP2; Paper V).

Tetraneopentylethylene was previously studied by Olah and Prakash[39] by means of dynamic NMR. Based upon NMR spectra, they suggest a conformation in which the alkyl groups project alternately up and down relative to the ethylene plane as the most stable one.

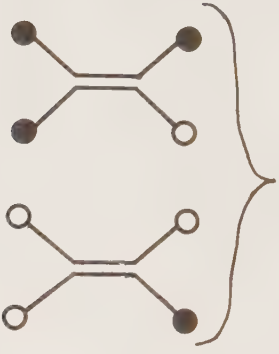
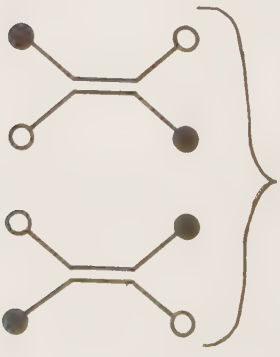
Tetrabenzylethylene was studied by Richardson and Gunderson,[40] and they suggest the most stable conformation to be the one with two trans benzyl groups lying in the same plane as the double bond and the other two up and down with respect to the double bond plane (Figure 5).

Figure 5. Minimum energy conformations, suggested by Richardson and Gunderson,[38] for compound 31.

In this thesis investigation of compounds 27-31 with dynamic ^{1}H NMR gave $\Delta G^{\ddagger}_{418} = 20.4 \pm 0.1$ kcal mol^{-1} for compound 30 and $\Delta G^{\ddagger}_{181} = 8.8 \pm 0.2$ kcal mol^{-1} for compound 29. The barriers to rotation for 27, 28, and 31 were too low to be measured.

Five possible conformations with perpendicular alkyl groups are listed in Table 5. The opened and filled circles denote alkyl groups pointing toward different sides of the double bond.[41] The notation for the various isomers is taken from Willem et al.[41] The conformations of the alkyl groups in compounds 27, 28, and 31 can not be determined from NMR

Table 5. Rotational isomers of tetra-primary-alkylethylenes, $(RCH_2)_2C{=}C(CH_2R)_2$.

Isomer	Structure	No. of R and CH_2 signals
I_4		1
I_3		4
$\bar{I}_3$		
I_{2c}		1
I_{2g}		1
I_{2t}		1
$\bar{I}_{2t}$		

spectra, and the only conformation that can be excluded for compounds 29 and 30 is $I_3/\bar{I}_3$. MM calculations were carried out in an attempt to predict the most stable conformation. The five conformations in Table 6 were calculated to be local energy minima. The conformation suggested by Richardson and Gunderson[40] for compound 31 was also calculated to be a local minimum, although higher in energy than I_{2g}. The calculations predict $I_{2t}/\bar{I}_{2t}$ to be the most stable conformation for 27, 28, 29, and 30, while I_{2g} is calculated to be the most stable conformation for compound 31. Figure 6 shows the calculated conformation

Table 6. Relative steric energies (kcal mol^{-1}) of the rotational isomers of 27-31 calculated by the MM2 (MMP2) force fields.

Compound	Conformers [a]				
	I_{2t}	I_3	I_4	I_{2c}	I_{2g}
27	0	1.74	1.78	1.87	2.14
28	0	1.76	1.71	2.48	2.18
29	0	6.71	5.33	2.95	7.04
30	0	11.38	23.43	12.42	17.85
31 [b]	2.72	3.76	3.44	4.23	0

[a] See Willem et al.[41] for conformational designations. [b] MMP2.

for compound 29. In order to get more information about the conformation for compound 31, the molecular structure was determined by X-ray analysis. The crystal structure was found to belong to the rotational isomer class I_{2t} (Figure 7) in contrast to the calculations.

To investigate the reason for the disagreement between calculation and experiment for compound 31 the potential energy curves for the perpendicular and parallel geometry for the benzene dimer as a function of the distance were calculated

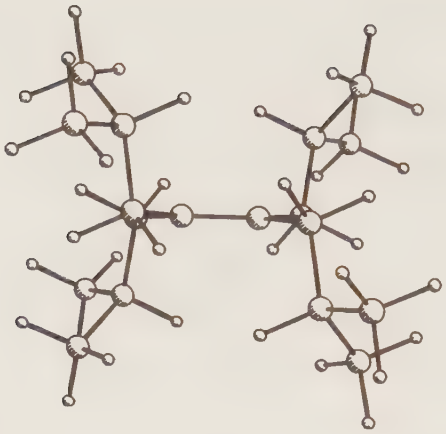


Figure 6. Minimum energy conformation of tetraisobutylethylene, 29, calculated by the MM2 force field.

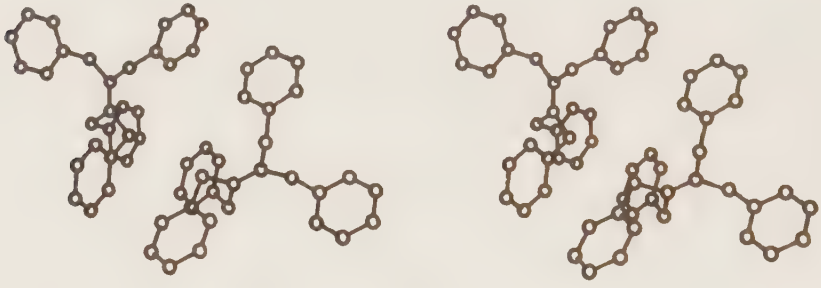


Figure 7. Stereoview of the X-ray structure of tetrabenzylethylene, 31.

with MMP2. Comparison of these curves with empirical[42] and *ab initio*[43] results shows that MMP2 predicts the parallel conformation to be the most stable one, in contradiction to the other computational methods.

The preference for the I_{2t} conformation in tetra-primary-alkylethylenes is most likely to be governed by a combination of steric repulsion between geminal and *cis*-alkyl groups and weak attractive steric effects for *trans*-alkyl groups. MM calculations indicate that attractive steric effects determine the conformations of *trans*-1,2-dialkylethylenes, leading to a

preference for syn conformation. The cis-1,2- and 1,1-dialkylethylenes show a preference for the anti conformation.

The rearrangement from I_{2t} to its enantiomer $\bar{I}_{2t}$ can proceed with rotation of one, two, three or four groups at a time. In order to choose between these mechanisms, molecular mechanics calculations (MM2) were performed for 27 and 29 using the incremental driving technique. According to the calculations, the rearrangement proceeds through a stepwise rotation of one group at a time with three intermediate local minima. Figure 8 shows the energy profile for compound 29. The rotation past the geminal neighbour showed a lower barrier than that past the vicinal neighbour. The calculated barrier heights are 3.7 kcal mol^{-1} for compound 27 and 8.8 kcal mol^{-1} for compound 29, in agreement with experiment. The barrier to rotation for compound 27 was too low to be measured and 8.8 kcal mol^{-1} for compound 29.

In the ground-state conformation both sides of the double bond are protected from attack. This is illustrated by a study of the reactivity of the ethylenes by epoxidation with m-chloro-perbenzoic acid in methylene chloride at 20 °C (Paper V). The relative rates were 1-octene: 0.4 ± 0.4, 27: 17 ± 5, 28: 16 ± 2, 29: 1.0, 31: 0.003 ± 0.001. Compound 30 reacted immeasurably slowly at 20 °C. The results may be summarized as two opposing effects:[44] (1) the rate is increased by the number of alkyl groups attached to the double bond, (2) the rate is decreased by branching of the alkyl groups.

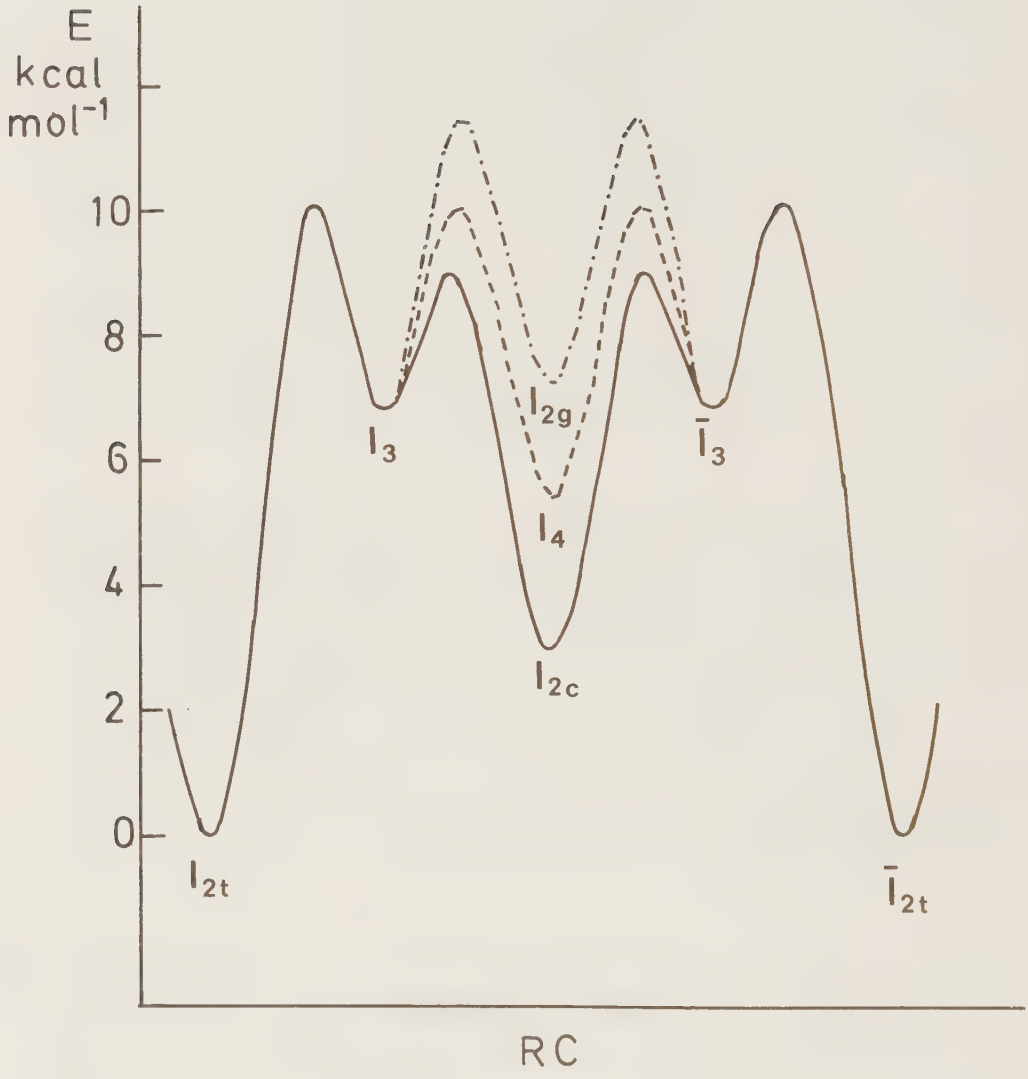


Figure 8. Potential energy curve for enantiomerization of 29 calculated by the MM2 force field. RC = reaction coordinate.

5. DISCUSSION

The effective steric size of a group depends on the non-bonded effects on its particular environment and on the measurement of these effects.

The effective steric size of a phenyl ring depends among other things on the framework to which it is attached, geometrical relationship to the framework, the shapes of its neighbours, and the geometrical relationships between the phenyl ring and the groups it interacts with. The results have been shown to fluctuate (Table 1), and further illustrations of this phenomenon have been presented in this work.

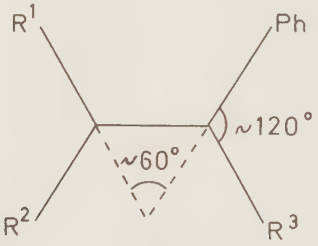
Systems of types 2 and 3 have some structural properties in common. The styrenes have a double bond between the α and β atoms, while the benzamides have an amide bond making up a fairly rigid sp^2-framework, structurally related to the styrenes. The length of the double bond in the styrenes and the amide bond is similar. This is also the case with the bond angles C=C-R and C=C-Ph in the styrenes and N-C=X and N-C-PH in the benzamides. The dihedral angle between the sp^2-skeleton and the phenyl ring is about the same in the two systems. In both the styrenes and the benzamides the isopropyl groups interact essentially with the "face" of the phenyl ring. As a consequence of these similarities the steric behaviour of the phenyl group is quite similar in the systems 2 and 3, as seen in Papers II and IV.

When a phenyl ring is attached to an sp^2-framework in a cis-vicinal position to an isopropyl group as in systems 2 and 3, its effective steric size, as indicated by the conformations of the isopropyl groups, is larger than H, C=O, iPr, Me, Et, C=S, C=Se and CH_2t-Bu but smaller than t-Bu.

When the phenyl ring and the alkyl group are attached to the same atom as in system 1, the effective steric size of the phenyl ring is smaller than that of a methyl group or any other alkyl group (Paper I).

One reason for this difference between the results from system 1 and systems 2 and 3 could perhaps be different geometrical relationship between the phenyl ring and the alkyl

groups it interacts with. The bond angle between Ph and R^3 is ca. 120° and the angle between Ph and R^1 ca. 60°. This causes a shorter distance between an atom of R^1 pointing towards the benzene ring and the phenyl ring than between an atom of R^3 pointing towards the benzene ring and the phenyl ring. This results in a stronger interaction between Ph and R^1 than between Ph and R^3, even though R^1 is vicinal to the phenyl ring.



Another type of system, in which the phenyl ring behaves as if it were small, is tetrabenzylethylene (31).

The effective size of a group depends among other things upon its neighbours and how well they fit together. Two isopropyl groups that interact have the possibility to assume a geared conformation. The phenyl ring and an isopropyl group do not have this possibility and the conformation in which an isopropyl group turns its bulkier side, the methyl groups, toward the phenyl ring, in a cis-vicinal arrangement, will be associated with considerable strain.

This work and the results presented in Table 1 show that a detailed analysis of each individual system is necessary to be able to estimate the steric effects of a particular group.

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PAPER I

Acta Chemica Scandinavica B 38 (1984) 397–405

Conformational Analysis of Crowded Anilides and Thioanilides. The "En-Face" Steric Effect of Aryl Groups

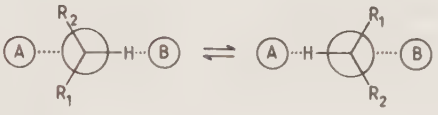
INGRID PETTERSSON and JAN SANDSTRÖM

Division of Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 740, S-220 07 Lund, Sweden

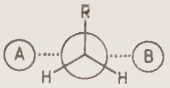
In order to study the interaction of isobutyl, neopentyl, and isopropyl groups with the "face" of aromatic rings, a series of *o,o'*-disubstituted anilides and thioanilides with the above-mentioned groups as *N*-substituents has been investigated by temperature-dependent NMR spectroscopy and by molecular mechanics calculations. The barriers to (thio)acyl group rotation were determined by bandshape and in one case also by stereomutation technique and were found in the range 86–104 kJ mol^{-1}. The barriers to aryl group rotation were studied in 2-chloro-6-methyl-(thio)anilides and were found to be at least 110 kJ mol^{-1}, thus permitting resolution in enantiomers.

The barriers to rotation of the *N*-alkyl groups were too low to be measured by NMR. Molecular mechanics calculations gave the preferred conformations of the neopentyl and isopropyl groups, and the results indicate that the aromatic ring face presents a very small hindrance to the rotation of these groups. The calculated *N*-alkyl group conformations are supported by a comparison of experimental shieldings with those calculated by the ring current model for the magnetic anisotropy of the aromatic ring.

In previous studies from this and associated groups, the conformations and barriers to rotation of primary [1–4] and secondary [5–7] alkyl groups attached to sp^2 hybridized frameworks have been studied by NMR bandshape technique and by empirical strain energy calculations. The alkyl groups have been placed between flanking groups, in which the main interaction either comes from one single atom (O, S, Se in C=O, C=S, C=Se, CH_3O, CH_3S or CH_3Se), or from a group of atoms (CH_3 or other alkyl groups). It has been found in all these cases (see also [8–10]) that secondary alkyl groups in general take up an orientation with the methine proton in or nearly in the sp^2 plane (*1*, parallel orientation [9]), whereas primary alkyl groups ($-CH_2R$) orient themselves with the C–R bond in a plane nearly perpendicular to the sp^2 plane (*2*).



1a *1b*



2

With secondary alkyl groups and unequal flanking groups A and B, two rotamers, *1a* and *1b*, are possible. The equilibrium constants, $K=[1b]/[1a]$, as well as the barriers to interconversion ($\Delta H^{\ddagger}$ or $\Delta G^{\ddagger}$) reflect the steric effects of A and B and can, with due circumspection,[3,4] be used to assess the relative sizes of substituent groups.

This study is part of a series intended to investigate the stereochemical behaviour and apparent size of an aromatic ring as a flanking group. The compounds studied are of the general type *3*.

In these, three kinds of rotational processes are feasible, *viz.*

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(1) rotation around the RCX–N bond (amide/thioamide rotation),
(2) rotation around the N–CHR_1R_2 bond, and
(3) rotation around the N–Ar bond.

The aim of this study is to find the minimum energy conformations, their populations and the barriers separating them with respect to these three rotational processes. For this purpose we have used NMR spectra and empirical strain energy (MMP1)[11,12] calculations.

It is evident that the part of the barrier to torsion around the N–Ar bond, which is due to conjugation, must be quite small, considerably less than the 23.9 kJ mol^{-1} found for aniline.[13] Therefore the aromatic ring must be readily rotated to respond to the steric requirements of the neighbouring groups. In order to have a reasonably well defined orientation of this ring perpendicular to the (thio)amide plane, 2,6-disubstituted aromatic rings were employed. In this way, the other groups will approach the aromatic ring from the planar side ("en face"), *i.e.* its steric effect will be determined by its π-electron cloud.

EXPERIMENTAL

Syntheses. All compounds of type *3* used in this study are found in Table 1 together with the thermodynamic data for the $E \rightarrow Z$ conversion. The anilides were prepared by conventional methods. Most thioanilides were prepared by refluxing the corresponding anilides with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphethane-2,4-disulfide ("the Lawesson reagent")[14] in toluene (method A). However, this method did not work with some hindered anilides, but in these cases thiation was achieved by reaction with diboron trisulfide, prepared *in situ* from bis(tricyclohexyltin) sulfide and boron trichloride according to Steliou and Mrani[15] (method B).

In all cases the final products were purified by preparative TLC (PTLC) on silica gel (Merck 60 F_{254}) with chloroform as solvent, or by preparative GLC (PGC), using 15 % OV-101, 45–60 mesh, in a 3 m column. The purity and identity of the compounds were assessed by ^1H NMR and mass spectra. The ^1H chemical shifts are found with assignment in Table 2.

N-*Neopentyl-2,6-dimethylacetanilide* (*4*). 2,6-Dimethylaniline (12.1 g, 0.10 mol) was added in portions to a stirred solution of pivaloyl chloride (6.0 g, 0.05 mol) in toluene (70 ml) at ambient temperature. After standing at ambient temperature for 1 h, the mixture was refluxed for 5 h, filtered and evaporated to give crude *2,6-dimethylpivalanilide* (3.7 g, 36 % yield) as colourless prisms, m.p. 167–169 °C. ^1H NMR (60 MHz, $CDCl_3$): δ 7.00 (3H, s), 2.13 (6H, s), 1.30 (9H, s).

This anilide (3.9 g, 0.019 mol) was added in portions to a solution of $LiAlH_4$ (0.9 g, 0.023 mol) in dry ether (50 ml). After 1 h at ambient temperature the mixture was refluxed for 26 h. After cooling, water (1 ml), 15 % NaOH (aq.) (1 ml) and water (3 ml) were added in this order. A white precipitate was removed by filtration (with suction), and the organic phase was dried with $MgSO_4$ and evaporated. Addition of hexane to the residue left unreacted starting material undis-

Table 1. Substituents in compounds *4–14* (see structure *3*), fractional population of the *E* form and $\Delta G^{\ddagger}$ for the $E \rightarrow Z$ exchange.

Compound	X	Y	Z	R	R^1	R^2	P_E[a]	$\Delta G^{\ddagger}_{E \rightarrow Z}$/kJ mol^{-1}
4	O	CH_3	CH_3	CH_3	H	$C(CH_3)_3$	1.00	–
5	S	CH_3	CH_3	CH_3	H	$C(CH_3)_3$	1.00	–
6	O	CH_3	CH_3	$C(CH_3)_3$	H	$C(CH_3)_3$	1.00	–
7	S	CH_3	CH_3	$C(CH_3)_3$	H	$C(CH_3)_3$	0.84	86.9
8	O	CH_3	Cl	$C(CH_3)_3$	H	$C(CH_3)_3$	1.00	–
9	O	CH_3	Cl	$C(CH_3)_3$	H	$CH(CH_3)_2$	1.00	–
10	S	CH_3	Cl	$C(CH_3)_3$	H	$CH(CH_3)_2$	0.69	89.4
11	O	CH_3	CH_3	H	CH_3	CH_3	0.92	102.5
12	S	CH_3	CH_3	H	CH_3	CH_3	0.44	103.8
13	O	CH_3	CH_3	CH_3	CH_3	CH_3	1.00	–
14	S	CH_3	CH_3	CH_3	CH_3	CH_3	1.00	–

[a] At +25 °C in *o*-dichlorobenzene.

solved, and evaporation of the hexane solution and distillation gave N-*neopentyl-2,6-dimethylaniline* as a liquid (2.0 g, 55 % yield), b.p. 87–90 °C/0.4 kPa. ^{1}H NMR (60 MHz, $CDCl_3$): δ 6.67–7.23 (3H, m), 2.93 (1H, broad), 2.67 (2H, s), 2.27 (6H, s), 1.03 (9H, s). Acetyl chloride (0.25 g, 0.003 mol) was added dropwise with stirring to a solution of the above aniline (0.6 g, 0.003 mol) in 1,2-dichloroethane (10 ml) with anhydrous sodium carbonate (0.4 g) at +10 °C. After reflux for 22 h the mixture was filtered hot and evaporated to give *4* (0.6 g, 86 % yield) as a colourless liquid, finally purified by PTLC. MS [IP 70 eV; *m/e* (% rel. int.)]: 233 (3, M), 218 (2, M–CH_3), 134 (100, M–CH_2CO–C_4H_9).

N-*Neopentyl-2,6-dimethylthioacetanilide* (*5*) was obtained from *4* in 59 % yield by method A as a pale yellow liquid, purified by PTLC. MS: 249 (6, M), 71 (100).

N-*Neopentyl-2,6-dimethylpivalanilide* (*6*) was prepared as *4* from *N*-neopentyl-2,6-dimethylaniline and pivaloyl chloride and was obtained in 57 % yield as colourless crystals, m.p. 67–68 °C. MS: 260 (1, M–CH_3), 57 (100, C_4H_9).

N-*Neopentyl-2,6-dimethylthiopivalanilide* (*7*) was obtained from *6* by method B in 40 % yield as pale yellow prisms, m.p. 81–82 °C. MS: 291 (4, M), 276 (3, M–CH_3), 71 (100).

N-*Neopentyl-2-chloro-6-methylpivalanilide* (*8*) was prepared analogously with *6*, starting from 2-chloro-6-methylaniline. The pivalanilide *8* was obtained in about the same yield as *6* as colourless prisms, m.p. 94–96 °C. MS: 280/282 (2.5/1.0, M–CH_3), 260 (3, M–Cl), 57 (100, C_4H_9).

N-*Isobutyl-2-chloro-6-methylpivalanilide* (*9*). N-*Isobutyl-2-chloro-6-methylaniline* was prepared in 71 % yield in the same way as *N*-neopentyl-2,6-dimethylaniline, starting from *2-chloro-6-methyl-butyranilide*. The pivalanilide *9* was obtained in 82 % yield analogously with *6* as colourless prisms, m.p. 53–54 °C. MS: 266/268 (2/1, M–CH_3), 246 (6, M–Cl), 57 (100, C_4H_9).

N-*Isobutyl-2-chloro-6-methylthiopivalanilide* (*10*) was obtained from *9* by method B in 39 % yield as pale yellow prisms, m.p. 54–56 °C. MS: 262 (5, M–Cl), 57 (100, C_4H_9).

N-*Isopropyl-2,6-dimethylformanilide* (*11*). The method described by Schellenberg[16] for the preparation of *N*-isopropylamines was adapted to N-*isopropyl-2,6-dimethylaniline,* which was obtained from 2,6-dimethylaniline as a colourless liquid in 61 % yield, b.p. 88–98 °C/3.7 kPa. ^{1}H NMR (60 MHz, $CDCl_3$): δ 6.5–7.2 (3H, m), 3.37 (1H, septet, *J* 7.0 Hz), 2.87 (1H, s), 2.23 (6H, s), 1.08 (6H, d, *J* 7.0 Hz).

Formylation with formic acetic anhydride according to Huffman[17] gave *11* as a colourless liquid in 98 % yield, finally purified by PGC.

Table 2. ^{1}H Chemical shifts[a] of alkyl groups in *4–14*.

Compound	ArCH_3	R	[R_1, R_2]	
4E	2.31	1.71 (CH_3)	3.45 (CH_2)	0.93 ($C(CH_3)_3$)
5E	2.26	2.23 (CH_3)	4.22 (CH_2)	0.97 ($C(CH_3)_3$)
6E	2.35	0.93 ($C(CH_3)_3$)	3.45 (CH_2)	0.93 ($C(CH_3)_3$)
7E	2.36	1.22 ($C(CH_3)_3$)	4.34 (CH_2)	0.98 ($C(CH_3)_3$)
7Z	2.18	1.61 ($C(CH_3)_3$)	4.04 (CH_2)	0.77 ($C(CH_3)_3$)
8E	2.34	1.02 ($C(CH_3)_3$)	3.29, 3.69 (CH_2)[b]	0.93 ($C(CH_3)_3$)
9E[c]	2.34	1.03 ($C(CH_3)_3$)	3.39, 3.43 (CH_2)[d]	1.96 (CH)[e] 0.93, 0.95 ($CH(CH_3)_2$)[f]
10E[c]	2.31	1.22 ($C(CH_3)_3$)	3.93, 4.23 (CH_2)[d,g]	1.87 (CH)[e] 0.93 ($CH(CH_3)_2$[f]
10Z[c]	2.71	1.57 ($C(CH_3)_3$)	3.86, 4.02 (CH_2)[d,h]	2.20 (CH)[e] 0.80, 0.91 ($CH(CH_3)_2$[f]
11E	2.18	7.74 (H)	4.19 (CH)	1.22 (CH_3)
11Z	2.24	8.28 (H)	3.71 (CH)	1.40 (CH_3)
12E	2.17	9.12(H)	5.07 (CH)	1.26 (CH_3)
12Z	2.16	9.53 (H)	3.84 (CH)	1.44 (CH_3)
13E	2.20	1.60 (CH_3)	4.39 (CH)	1.12 (CH_3)
14E	2.15	2.14 (CH_3)	5.37 (CH)	1.18 (CH_3)

[a] In ppm, downfield from TMS. Solvent $CHCl_2F$+$CHClF_2$ unless otherwise stated, ambient temperature. [b] AB system. [c] Solvent $CDCl_3$. [d] AB part of an $ABMX_6$ system. [e] M part of an $ABMX_6$ system. [f] X part of an $ABMX_6$ system. [g] J_{AB}=13.2 Hz. [h] J_{AB}=14.1 Hz.

MS: 191 (78, M), 176 (46, M−CH_3), 148 (100).

N-*Isopropyl-2,6-dimethylthioformanilide* (*12*) was obtained from *11* by method A in 40 % yield as pale yellow prisms, m.p. 77–79 °C. MS: 207 (48, M), 192 (13, M−CH_3), 132 (100).

N-*Isopropyl-2,6-dimethylacetanilide* (*13*) was prepared from *N*-isopropylaniline analogously to *4* in 81 % yield as a colourless liquid, finally purified by PTLC. MS: 205 (12, M), 190 (3, M−CH_3), 84 (100).

N-*Isopropyl-2,6-dimethylthioacetanilide* (*14*) was obtained in 82 % yield from *13* by method A. Pale yellow prisms, m.p. 54–56 °C. MS: 221 (18, M), 146 (100).

Variable-temperature ^1H NMR spectra were recorded on a JEOL model MH-100 NMR spectrometer equipped with a standard variable temperature attachment (VT 3-c). The samples for low temperature studies were *ca* 0.5 M in a mixture of dichlorofluoromethane and chlorodifluoromethane (FREON 21 and 22, *ca* 1:1), and they were degassed by repeated cycles of freeze-thawing before being sealed off under high vacuum. Tetramethylsilane was added with the solvent to provide the internal lock signal. High temperature spectra were recorded on solutions in *o*-dichlorobenzene with octamethylcyclotetrasiloxane for the lock. The temperatures were measured by monitoring the voltage of the internal thermocouple of the instrument and calibrating it at each experiment against an external thermocouple placed in a dummy tube containing the appropriate solvent.

The populations and rate constants were evaluated by visual fitting of the experimental spectra to spectra calculated by the McConnell formalism for uncoupled two-site exchange systems.[18,19] The calculations were performed on a PDP 11/34 computer with a GT 42 graphics terminal and a Printronix lineprinter/plotter of the Computer Graphics Laboratory for Organic Chemistry of the University of Lund.

The evaluation of T_2 values for bandshape calculations was based on the bandwidths of reference signals unperturbed by exchange as described previously.[20]

Table 3. Force field parameters.

Torsional constants Angle	V_1	V_2	V_3/kJ mol^{-1}
C−C−N(sp^2)−C(sp^2)	0.00	0.00	4.19
H−C−N(sp^2)−C(sp^2)	0.00	0.00	4.19
S=C−N(sp^2)−C(sp^2)	0.00	25.12	0.00
C−C_{CO}−N(sp^2)−C(sp^2)	0.00	25.12	0.00
C(sp^2)−C(sp^2)−N(sp^2)−C	0.00	0.00	0.00
C(sp^2)−C(sp^2)−N(sp^2)−C_{CO}	0.00	0.00	0.00
C−C(sp^2)−C(sp^2)−N(sp^2)	0.00	68.04	0.00
C(sp^2)−C(sp^2)−C(sp^2)−N(sp^2)	0.00	68.04	0.00
N(sp^2)−C−C−C	0.00	0.00	2.22
H−C−C=S	0.00	0.00	−5.23
S=C−N(sp^2)−C	0.00	25.12	0.00

Stretching constants Bond	L_o/Å	k_s/mdyn Å^{-1}
C(sp^2)−N(sp^2)	1.449	3.40
C=S	1.626	5.14

Bending parameters Angle	θ_o/deg.	k_b/mdyn Å rad^{-2}
C(sp^2)−C(sp^2)−N(sp^2)	120.0	0.60
C(sp^2)−N(sp^2)−C_{CO}	121.0	0.70
C−N(sp^2)−C(sp^2)	115.0	0.50
H−C=S	125.0	0.25
N(sp^2)−C=S	125.0	0.50
C−C=S	122.3	0.40
C=S	0.00	0.80

The free energies of activation were calculated using eqn. 1, which is based on the Eyring equation.[21]

$$\Delta G^{\ddagger}_{E\rightarrow Z}=1.914\cdot 10^{-2}T[10.319+\log(T/k_{E\rightarrow Z})] \quad (1)$$

The $E\rightarrow Z$ stereomutation of *12* was studied by monitoring the integrals of the thioformyl proton resonances as a function of time. The rate constant $k_{E\rightarrow Z}$ was evaluated from a least-squares semilogarithmic plot based on eqn. 2, using also eqn. 3,[22] where $I_{E,0}$ $I_{E,t}$, and $I_{E,e}$ represent the relative integrals of the E proton resonance at $t=0$, t, and ∞. At 47.0 °C, $k_{E\rightarrow Z}=(6.7\pm0.5)\cdot 10^{-5}$ s^{-1}.

$$(k_{E\rightarrow Z}+k_{Z\rightarrow E})t=\ln\frac{I_{E,0}-I_{E,e}}{I_{E,t}-I_{E,e}} \quad (2)$$

$$K=\frac{k_{Z\rightarrow E}}{k_{E\rightarrow Z}}=\frac{I_{E,0}-I_{E,e}}{I_{E,e}} \quad (3)$$

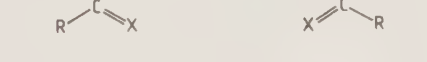
The molecular mechanics calculations were performed using the program developed by Allinger and co-workers with their 1973 force field (MMP1).[11,12] The parameters describing the (thio)amide skeleton were those used successfully for the calculation of ground state energies[1,6,23] and rotational barriers[24] in relatively strained amides and thioamides. The parameters not given previously are found in Table 3.

RESULTS AND DISCUSSION

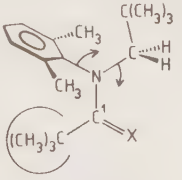
Shvo *et al.*[25] have studied a series of compounds (*15*), which show similarities with those in our work. In *15*, R=H, alkyl or aryl, and in all compounds except the formamide, only one rotamer is observed. This is shown by the aromatic solvent induced shift (ASIS)[26,27] method to be the *E* form, and also in the formamide this form dominates strongly. Similar compounds have been studied by Siddall and Stewart[28] with equivalent results. *N*-Methylacetanilide has been shown by NMR spectroscopy[29] and X-ray crystallography[30] to be predominantly (99.5 % in solution, exclusively in the crystal) in the *E* form with the benzene ring orthogonal to the amide plane.

Several authors[29,31,32] have reported considerable shift differences for the acyl group protons in the *E* and *Z* forms of anilides, with the *E* form resonances in general at higher field. Rae[33] has shown that increased deviation from coplanarity of the aromatic ring increases the shift difference in a series of ortho-substituted formanilides because of increased shielding in the *E* form, a result which is supported by model calculations using the shielding data of Johnson and Bovey.[34] However, in some formanilides the formyl proton in the *E* form is *less* shielded than that in the *Z* form.[32,35]

The assignment of *E* and *Z* rotamers in the compounds *4–14* is mostly straightforward. It can be based on the shifts of the R protons, and as references we have used the shifts in the analogous *N,N*-diisopropyl-[6] and *N,N*-dineopentyl- and -isobutyl(thio)amides,[1] when available. In the afore-mentioned compounds, the acetylmethyl proton resonances fall in the narrow range of δ 2.01–2.15 with the higher values for the more crowded environments. The corresponding range for thioacetamides is δ 2.63–2.79. The acetyl ^{1}H resonances in *4* and *13* fall at δ 1.71 and 1.60. Thus these rotamers are assigned to the respective *E* forms. Similarly, the thioacetyl ^{1}H resonances in *5* and *14* fall at δ 2.23 and 2.14, and must also be ascribed to the *E* form. The ^{1}H resonances of the (thio)pivaloyl groups in *N,N*-diisopropyl pivalamide and -thiopivalamide fall at δ 1.26 and *ca* 1.40 respectively,[24] and the compounds with more shielded t-Bu protons (*6*, *8*, major rotamer of *7* and minor rotamer of *10*)



3 E *3 Z*



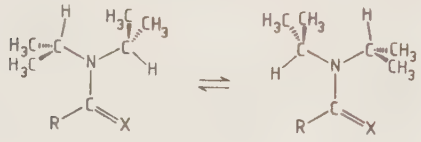
6 E, X = O
7 E, X = S

are assigned to the *E* form. To support these conclusions, the ring current shieldings of acetyl and pivaloyl protons in *E* forms of the (thio)acet-

and (thio)pivalamides were calculated, using the tables of Haigh and Mallion.[36] The geometric data required were taken, for the (thio)acetanilides from the MMP1 energy-minimized structure of *5E* (*vide infra*), and for the (thio)pivalanilides from a standard geometry (standard bond lengths from MMP1, all angles at sp^2 atoms 120° and at sp^3 atoms 109.5°). For the (thio)acetyl protons an average shielding of 0.14 ppm and for the (thio)pivaloyl protons one of 0.17 ppm was calculted, in general somewhat less than but of the same order of magnitude as the observed differences between the *N,N*-dialkyl(thio)amides and the corresponding *E*-(thio)anilides.

All compounds, which show two rotamers with respect to the CX−N bond (*7, 10, 11,* and *12*) were studied both in FREON and in *o*-dichlorobenzene as solvent. Without exception, the resonances of the ring methyl and *N*-alkyl protons being *anti* to the (thio)carbonyl group with respect to the CX−N bond showed larger upfield shifts in the aromatic solvent than those being *syn*, thus supporting the assignments made in Tables 1 and 2.

N,N-Diisopropylamides and -thioamides normally exist as mixtures of two major rotameric forms *16A* and *16B*. The equilibrium between

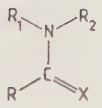


16 A *16 B*

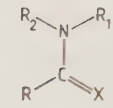
them is shifted toward the *B* form by increasing size of R or decreasing size of X, and from the position of the equilibrium a scale of relative sizes of a series of R and X can be established. The scale emerging from compounds *16* can be given as:[6,7,37]

$$H \simeq O < iPr < CH_3 \simeq S < tBu$$

The scale can be used to assess the steric requirements of different groups R^1 and R^2 in other *N,N*-disubstituted {thio}amides *17*. Here, the larger of R and X will prefer to be on the same side of the C^1-N bond as the smaller of R^1 and R^2. In this way we can establish that R^1=aryl is smaller than methyl and other alkyl groups,



17 A



17 B

since already in *N*-methylacetanilide the *E* form is 99.5 % of the equilibrium mixture.[29] This is also in agreement with the dominance of the *E* form in all anilides in this work, and also in that reported in Refs. 25 and 28.

However, with the thioanilides, the situation is not quite so straightforward. In the thioformanilide *12* the *Z* form dominates, but in the thioacetanilides *5* and *14* only the *E* forms can be observed, as is also the case with *N*-benzyl-*o*-methyl-thioacetanilide.[28] When the size of the R group is increased, as in *7* and *10*, the *Z* form appears again. In the standard geometry used to calculate the shielding in the *E* form of *7*, the shortest distance between a hydrogen atom in the pivaloyl group and a carbon atom in the benzene ring is 220 pm, compared to 335 pm for the sum of the van der Waal's radii. Clearly a considerable repulsion must occur also in the *E* form, and the balance of the repulsions on both sides of the C^1-N bond leads to a relative favorization of the *Z* form. This is not observed in the analogous pivalanilide *6*, possibly because the smaller oxygen atom permits a larger deflection of the *N*-neopentyl group and the benzene ring away from the pivaloyl tBu group than can occur in *7*. Similar considerations apply to *9* and *10*.

The free energy barriers to rotation of the thiopivaloyl group in *7* (87 kJ mol^{-1}) and *10* (89.5 kJ mol^{-1}) reveal some ground-state strain, whereas the high barriers in *11* and *12* indicate essentially unstrained ground states but possibly strained transition states. The barrier in *12* is high enough to allow the separation of the *E* form in pure state by chromatography on silica. The rate of $E \rightarrow Z$ transformation could then be followed by direct stereomutation at 47 °C. The barrier thus measured shows no difference from the one measured by bandshape analysis at 176 °C, indicating an activation energy close to zero.

The isolation of pure $E-Z$ rotamers from 2,6-disubstituted anilides and thioanilides has been reported previously.[31,38]

We now come to the question of the conformations of the *N*-alkyl groups, and we begin with the

N-neopentyl compounds *4* to *8*. If the neopentyl group assumes a perpendicular or nearly perpendicular orientation with respect to the (thio)amide plane, the methylene protons are diastereotopic, and their ^{1}H NMR spectrum should appear as an AB system on slow rotation.[1] This is not observed in the available temperature region (≥ -130 °C) except for compound *8*, where the anisochrony is ascribed to the chiraly caused by slow rotation of the 2-methyl-6-chlorobenzene ring (*vide infra*). In compounds *4* to *7* the methylene protons have the (thio)amide plane as a time-average plane of symmetry, and this may arise because of fast exchange between two enantiomeric, more or less perpendicular orientations or because the molecule exists in one single energy minimum with a plane of symmetry. Since the NMR spectra give little information on this, we have performed MMP1 calculations on *5E* with special consideration of the effect of rotation around the N–CH_2 bond. The lowest energy minimum (total strain energy 66.3 kJ mol^{-1}) is found for a conformation with the benzene ring perpendicular to the thioamide plane and with the neopentyl group symmetrically bisected by this plane and *anti* to the thiocarbonyl group (Fig. 1). Rotation by *ca.* 40° in either direction leads to maxima 12.9 kJ mol^{-1} above the lowest minimum, and then at *ca.* ±90° rotation two enantiomeric minima are found only 0.9 kJ mol^{-1} above the lowest minimum. On continued rotation, the energy increases to a maximum of *ca.* 30 kJ mol^{-1} above the lowest minimum, when the *t*-butyl group eclipses the thiocarbonyl group.

Similar calculations on *5Z* gave a pair of minima at *ca.* ±90° rotation with a total strain energy of 78.5 kJ mol^{-1} (12 kJ mol^{-1} above the *E* form), supporting the assignment of the *E* conformation to the only observed rotamer.

The ring-current shielding of the *t*-Bu group in *5E* is calculated to be 0.14 and 0.03 ppm, respectively, for the minima, and the population-weighted mean is 0.08 ppm. In agreement with this, the *t*-Bu proton resonance appears at δ 0.97 compared to δ 1.08 for the similarly situated neopentyl group in *N,N*-dineopentylthioacetamide.[1]

The very strong shielding of the neopentyl *t*-Bu protons in *7Z* (δ 0.77) is best exlained by a deformation due to the proximity of the thiopivaloyl *t*-Bu group, which pushes the *N*-neopentyl group into a more strongly shielding region closer to the aromatic ring.

The situation with respect to rotation of the isopropyl groups in compounds *11* to *14* is similar. No splitting of the isopropyl resonances due to slow rotation about the N–iPr bond can be observed above −130 °C. MMP1 calculation of the energy of *12E* as a function of the H–$C(CH_3)_2$–N–CHS dihedral angle gave a very flat energy curve with the two deepest minima at angles of ±45° from the state where the iPr methine proton eclipses the thiocarbonyl group (Fig. 2), and a second pair of minima, 4.9 kJ mol^{-1} higher, at ±160°. The pair of highest energy maxima, 16.4 kJ mol^{-1}, is found at ±110°, *i.e.* in states where one of the iPr methyl groups nearly eclipses the thiocarbonyl group. In the ±45° conformation, the methine proton is still in the strongly deshielding region of the thiocar-

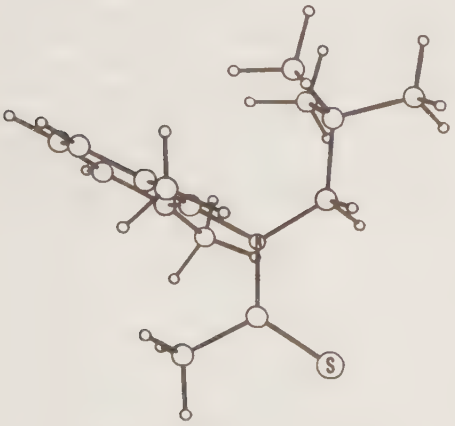


Fig. 1. Minimum energy conformation of *5E*.

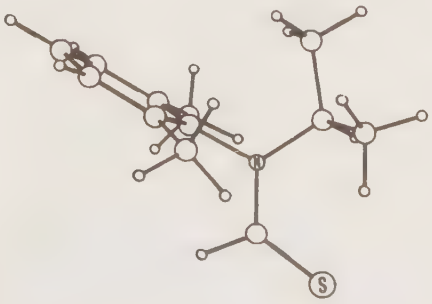
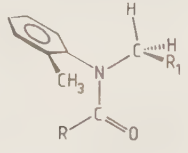


Fig. 2. Minimum energy conformation of *12E*.

bonyl group,[39] which fits with its resonance at δ 5.07, compared to 3.84 in *12Z* and 5.67 for the methine proton eclipsing the thiocarbonyl group in *N,N*-diisopropylthioformamide (*16B*, R=H, X=S).[6]

Calculations for *12Z* gave two pairs of energy minima, with the H−CMe_2−N−CSH dihedral angle at ±47 and at ±168°. The former minima are the lowest by 1.9 kJ mol^{-1}, and they are also 3.7 kJ mol^{-1} lower than the lowest minima in *12E*. Thus the calculations support the assignment of the low energy rotamer of *12* to the *Z* form. It also appears from the calculations that the face of the aromatic ring presents little hindrance to the rotation of the isopropyl group in *12* (and presumably even less in *11*).

The third type of process, the rotation of the aromatic ring, can for symmetry reasons only be observed in the 2-methyl-6-chloroanilides *8, 9,* and *10*. In *8* the neopentyl methylene proton resonance appears as an AB quartet, and in *9* and *10* the isobutyl methyl proton resonances appear as doublets of doublets, and the methylene proton resonances as the AB parts of a ABM system. None of these groups of signals shows any discernable band broadening due to exchange below +170 °C, which means that the rate constants for rotation of the aryl groups are less than 1 s^{-1} at this temperature. This gives a lower limit to the free energy to the rotation of 110 kJ mol^{-1}, corresponding to a half-life at +25 °C in excess of 24 d. Consequently, these compounds should be resolvable in optical antipodes, which has also been demonstrated by chromatography on microcrystalline triacetylcellulose. We will report on the resolution, the CD spectra, and the rates of racemization of these compounds in a forthcoming publication.



15 E

The barrier to rotation of the *o*-totyl ring in *N*-benzyl-2-methylacetanilide (*15E*, R=CH_3) is 84 kJ mol^{-1},[25] and in the analogous formamide the corresponding barriers are 54 kJ mol^{-1} and 42 kJ mol^{-1} in the *Z* and *E* forms, respectively.[28] In 2,6-diisopropylacetanilide (*18*), the barriers to rotation of the aromatic ring are 79 and 49 kJ mol^{-1} in the *E* and *Z* forms, respectively.[40] Similar barriers are found in other secondary 2,6-diisopropyl(thio)anilides, whereas the tertiary analogues have $\Delta G^{\ddagger} > 100$ kJ mol^{-1}.[41] Evidently the high barriers in the latter compounds as well as in *8, 9,* and *10* are due to the necessity for the simultaneous passage of one ortho substituent past the (thio)acetyl group and the other past the *N*-substituent.

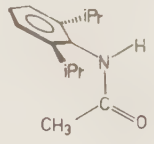
CONCLUSION

The result of this study is that primary alkyl groups attached to an sp^2 hybridized nitrogen atom with a (thio)acyl group and a 2,6-disubstituted aromatic ring as flanking groups may take up the customary perpendicular orientation (*2*), but that a conformation with R pointing towards the face of the aromatic ring is about equally probable even in the case when R=*t*-Bu. The barrier between these two conformations is quite low.

For isopropyl groups, the stable conformation is not the symmetrical bisected one (*1*), but one with less symmetry, in which the methyl groups point in the direction of the aromatic ring.

For both types of substituents, the face of the aromatic ring presents a small hindrance to the motion of adjacent alkyl groups.

This is in agreement with previous observations of the conformational dependence of the size of an aromatic ring. Thus, the ΔG°_{x} value for a phenyl group in cyclohexane is larger than that of a methyl group (12.5 *versus* 7.1 kJ mol^{-1}).[42] The high energy of the axial phenyl group is probably due to "edge-on" interactions between the ortho protons and the equatorial protons in positions 2 and 6 in a conformation, in which the phenyl group is perpendicular to the 1-CH bond. In a parallel conformation, strong interactions



18E

between the ortho protons and the axial 3-H and 5-H atoms would have given an even higher energy.[9] In 2,2-dimethyl-3-substituted butanes on the other hand, the steric effect of a 3-phenyl ring on the rotation of the *t*-butyl group is *smaller* than that of a 3-methyl group, at least partly because the *t*-butyl group rotates against the face of the phenyl ring.[43]

Acknowledgements. We are grateful to the Swedish Natural Science Research Council for financial support, to Docent Tommy Liljefors for advice with the molecular mechanics calculations, and to F.K. Kristina Stenvall for valuable preparative assistance.

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PAPER II

Correspondence and proofs should be sent to:
Dr. Ulf Berg, Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 740, S-220 07 Lund, Sweden

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Conformational Analysis of α-Alkyl-β,β-di-isopropylstyrenes. A Dynamic ^{1}H N.m.r. and Molecular Mechanics Investigation

Ingrid Pettersson and Ulf Berg*

Division of Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 740, S-220 07 Lund, Sweden

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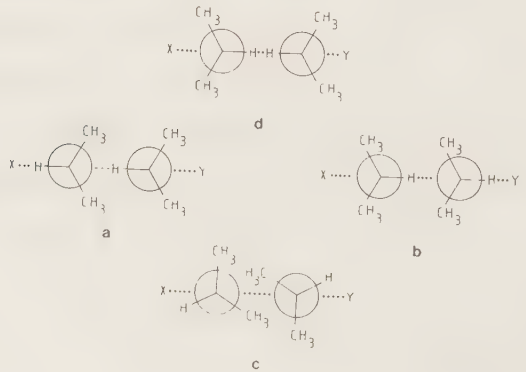
The conformational equilibria and barriers to rotation in α-R-β,β--di-isopropylstyrenes with R = H, Me, Et, Pr^i, CH_2Bu^t and Bu^t, and in tri-isopropylethylene and 1,1,2-tri-isopropylpropene investigated by dynamic ^{1}H n.m.r. and molecular mechanics (MM2, MMP2 force fields) are reported. The following conclusions are drawn: (i) the phenyl group is twisted ca. 70-90° out of the ethylene plane, (ii) the conformational populations of the geminal isopropyl groups indicate that the effective steric size of the phenyl group is larger than that of methyl, ethyl, isopropyl and neopentyl groups, but smaller than that of the t-butyl group, (iii) barriers ($\Delta G^{\ddagger}$) to interchange of the isopropyl groups fall in the range 10.5-12.2 kcal mol^{-1}, (iv) molecular mechanics calculations fail to reproduce the experimentally determined conformational populations but satisfactorily reproduce the barriers to rotation of the isopropyl and phenyl groups. According to these calculations the isopropyl group rotations are not correlated.

The stereochemistry of styrenes is highly dependent upon the substitution pattern in the α and β positions. While styrene is a planar molecule with a barrier of ca. 3 kcal mol^{-1} to rotation about the phenyl to olefin bond,[1] derivatives substituted in the α and β positions are twisted about the C-Ph bond, with substantial torsional barriers through a planar transition state.[2,3] Further substitution in one ortho position leads to chiral molecules with high optical stability.[4,5] This behaviour is a manifestation of the steric anisotropy of the phenyl group. The spatial requirement of aromatic rings has been examined in several cases and, not surprisingly, very divergent results have been obtained. This depends, among other factors, on the conformation of the aromatic ring, since the effective size of such a ring is quite different laterally and orthogonally.

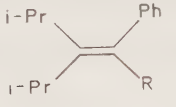
Isopropyl groups attached to a planar framework usually assume two well defined conformations with the C-H bond eclipsing the sp^2 plane, and two adjacent isopropyl groups exist in four general types of rotamers, a-d (Scheme 1), of which the two "gear-meshed" conformations a and b are in most cases lowest in energy.[6]



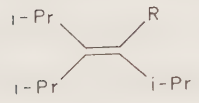
Scheme 1

The equilibrium between the rotamers is determined by the effective sizes of X and Y, and the study of the equilibrium constant offers a way to obtain information about the relative sizes of these groups.

We report here a ^1H n.m.r. and molecular mechanics investigation of a series of α-R-β,β-di-isopropylstyrenes (Scheme 2) in which the



R	
H	*1*
CH_3	*2*
C_2H_5	*3*
$(CH_3)_2CH$	*4*
$(CH_3)_3CH_2$	*5*
$(CH_3)_3C$	*6*



R	
H	*7*
CH_3	*8*

Scheme 2

phenyl group is twisted relative to the ethylene plane and where the face of the phenyl group is exposed to its flanking isopropyl group.

The two simple ethylene derivatives 7 and 8 were studied for comparison, and one derivative of 4, selectively deuterated on the isopropyl group geminal to the phenyl, was prepared as an aid in n.m.r. assignments.

Experimental

Syntheses.— The compounds were prepared by reductive coupling of the pertinent ketones with low-valent titanium reagent according to the method of McMurry and coworkers[7,8] or its modifications.[9,10]

If not stated otherwise, the procedure of Dams[9] was followed. Complicated product mixtures of various coupled products as well as reduced ketones (alcohols, hydrocarbons and pinacols) were obtained. In all cases the desired compound was isolated and purified by preparative g.c. (OV 101, 40-60 mesh, 3 m).

β,β-Di-isopropylstyrene (1) was prepared from 2,4-dimethyl-3-pentanone (2.85 g, 0.025 mol) and benzaldehyde (2.65 g, 0.025 mol) in 10 % yield (g.l.c.).

1-Benzyl-1-isopropyl-2-methylpropanol was prepared from benzylmagnesiumchloride (from benzylchloride (25.3 g, 0.20 ml) and magnesium (4.8 g, 0.20 mol)) and 2,4-dimethyl-3-pentanone in diethyl ether giving 39 g (94 %) of a colourless liquid, b.p.$_{0.9}$ 95-100 °C. δ_H (60 MHz; $CDCl_3$) 7.22 (5 H, s), 2.82 (2 H, s), 1.93 (3 H, br. sept., J = 7.0 Hz), 0.98 (6 H, d, J = 7.0 Hz), 0.90 (6 H, d, J = 7.0 Hz). ν_{max} 3580 (OH), 3500 (OH), 3080, 3060, 3020, 2960, 2880, 1940, 1970, 1800, 1700, 1600 cm^{-1}. m/e 188 (M−H_2O, 2 %), 163 (9), 145 (7), 119 (9), 115 (40), 105 (6), 97 (6), 91 (74), 77 (6), 71 (100), 65 (15), 59 (14), 55 (30), 51 (7), 45 (32).

β,β-Di-isopropylstyrene (1) was prepared from 1-benzyl-1-isopropyl-2-methylpropanol and "Amberlyst" 15 in methylene chloride at room temperature in almost quantitative yield. ν_{max} 3080, 3060, 3020, 2960, 2930, 2870, 1640, 1600, 1570, 1490, 1460, 1440 cm^{-1}. m/e 188 (M^+, 5 %), 145 (100), 131 (12), 117 (17), 105 (8), 91 (25), 77 (8), 65 (6), 51 (7). δ_H (360 MHz; [$^2H_6$]dimethyl ether) 1.05 (6 H, d, J = 6.8 Hz), 1.20 (6 H, d, J = 6.8 Hz), 2.50 (1 H, sept., J = 6.8 Hz), 3.10 (1 H, sept., J = 6.8 Hz), 6.40 (1 H, s), 7.1-7.3 (5 H, m).

β,β-Di-isopropyl-α-methylstyrene (2) was prepared from 2,4-dimethyl-3-pentanone (5.7 g, 0.050 mol) and acetophenone (6.0 g, 0.050 mol). ν_{max} 3080, 3060, 3010, 2960, 2930, 2870, 1600, 1490, 1460, 1440 cm^{-1}. m/e 202 (M^+, 9 %), 159 (100), 145 (14), 128 (19), 117 (83), 105 (22), 91 (29), 77 (22), 61 (12), 55 (22). δ_H (360 MHz; [$^2H_6$]dimethyl ether) 0.86 (6 H, d, J = 6.8 Hz), 1.27 (6 H, d, J = 6.8 Hz), 1.96 (3 H, s), 2.49 (1 H, sept., J = 6.8 Hz), 2.57 (1 H, sept., J = 6.8 Hz), 7.0-7.3 (5 H, m).

α-Ethyl-β,β-di-isopropylstyrene (3) was prepared from 1-phenyl--1-propanone (1.41 g, 0.0105 mol) and 2,4-dimethyl-3-pentanone (1.2 g, 0.0105 mol) in 25 % yield (g.l.c.). ν_{max} 3080, 3060, 2960, 2930, 2870, 1600, 1490, 1460, 1440 cm^{-1}. m/e 216 (M^+, 8), 173 (54), 145 (17), 131 (80), 117 (31), 105 (12), 97 (5), 91 (44), 77 (15), 65 (9), 57 (100). δ_H (360 MHz; [$^2H_6$]dimethyl ether) 0.83 (3 H, t, J = 7.2 Hz), 0.86 (6 H, d, J = 6.9 Hz), 1.29 (6 H, d, J = 6.9 Hz), 2.43 (2 H, q, J = 7.2 Hz), 2.42 (1 H, sept., J = 6.9 Hz), 2.60 (1 H, sept., J = 6.9 Hz), 7.0-7.3 (5 H, m).

α,β,β-Tri-isopropylstyrene (4) was prepared from 2,4-dimethyl--3-pentanone (2.85 g, 0.025 mol) and 2-methyl-1-phenyl-1-propanone (3.7 g, 0.025 mol) in 15 % yield (g.l.c.), m.p. 86-87 °C. ν_{max} 3080, 2960, 2930, 2870, 1600, 1460, 1440 cm^{-1}. m/e 230 (M^+, 8), 187 (28), 145 (68), 131 (34), 117 (21), 105 (22), 91 (42), 77 (15), 67 (11), 57 (100). δ_H (360 MHz; [$^2H_6$]dimethyl ether) 0.82 (6 H, d, J = 6.9 Hz), 0.89 (6 H, d, J = 6.9 Hz), 1.30 (6 H, d, J = 6.9 Hz), 2.23 (1 H, sept., J = 6.9 Hz), 2.57 (1 H, sept., J = 6.9 Hz), 3.23 (1 H, sept., J = 6.9 Hz), 6.9-7.3 (5 H, m).

2-[^{2}H]-2-Methyl-1-phenyl-1-propanone. D_2O (1.0 ml) and 2-methyl--1-phenyl-1-propanone (4.4 g, 0.030 mol) was added to CD_3OD (5 ml) and a catalytic amount of sodium. The mixture was allowed to stand with stirring at room temperature for 24 h and was then poured into D_2O. The solution was extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated to give a liquid, yield 3.5 g (80 %). δ_H (60 MHz; $CDCl_3$) 1.17 (6 H, s), 7.17-8.17 (5 H, m).

α-(2-[^{2}H])-Isopropyl-β,β-di-isopropylstyrene ([^{2}H]-4) was prepared from 2-[^{2}H]-2-methyl-1-phenyl-1-propanone (3.5 g, 0.024 mol) and 2,4-dimethyl-3-pentanone (2.7 g, 0.024 mol) in 17 % yield (g.l.c.), m.p. 85-86 °C. δ_H (360 MHz; [$^2H_6$]dimethyl ether) 0.82 (6 H, d, J = 7.0 Hz), 0.88 (6 H, s), 1.30 (6 H, d, J = 7.0 Hz), 2.24 (1 H, sept., J = 7.0 Hz), 2.58 (1 H, sept., J = 7.0 Hz), 6.9-7.3 (5 H, m).

3,3-Dimethyl-1-phenyl-1-butanone was prepared from phenyl magnesium bromide (from magnesium (2.4 g, 0.1 mol) and bromobenzene (15.7 g, 0.1 mol)) and 3,3-dimethylbutyryl chloride (13.4 g, 0.1 mol) in ether in 22 % yield, $b.p._{15}$ 132-133 °C. m/e 176 (M^+, 4 %), 120 (48), 105 (100), 77 (57), 57 (20), 51 (29). δ_H (60 MHz; $CDCl_3$) 1.07 (9 H, s), 2.83 (2 H, s), 7.2-8.0 (5 H, m).

β,β-Di-isopropyl-α-neopentylstyrene (5) was prepared from 3,3-dimethyl-1-phenyl-1-butanone (3.6 g, 0.020 mol) and 2,4-dimethyl--3-pentanone (2.1 g, 0.018 mol) in 23 % yield (g.l.c.). ν_{max} 3080, 3060, 3010, 2950, 2870, 1600 cm^{-1}. m/e 258 (M^+, 3 %), 215 (7), 159 (19), 145 (26), 131 (9), 117 (9), 105 (9), 91 (15), 83 (9), 69 (10), 65 (6), 57 (100). δ_H (360 MHz; [$^2H_6$]dimethyl ether) 0.73 (9 H, s), 0.88 (6 H, d, J = 7.2 Hz), 1.24 (6 H, d, J = 7.2 Hz),

2.51 (2 H, s), 2.62 (1 H, sept., J = 7.2 Hz), 2.83 (1 H, br. sept.) 7.10-7.15 (5 H, m).

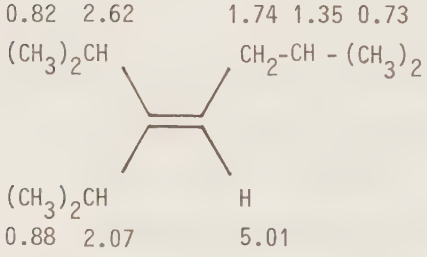
α-t-Butyl-β,β-di-isopropylstyrene (6) was prepared from 2,4-dimethyl-3-pentanone (2.85 g, 0.025 mol) and 2-dimethyl-1-phenyl--1-propanone (4.4 g, 0.0275 mol) in 4 % yield (g.l.c.). m/e 244 (M^+, 1 %), 201 (8), 159 (19), 145 (35), 131 (14), 117 (12), 105 (15), 91 (26), 77 (8), 69 (9), 57 (100). δ_H (360 MHz; [$^2H_6$]dimethyl ether) 0.78 (6 H, d, J = 7.1 Hz), 1.08 (9 H, s), 1.13 (6 H, d, J = 6.8 Hz), 2.39 (1 H, sept., J = 7.1 Hz), 3.47 (1 H, sept., J = 6.8 Hz), 6.9-7.2 (5 H, m).

3-Isopropyl-2,5-dimethyl-3-hexene (7) was prepared from 2-methyl--propanal (2.2 g, 0.030 mol) and 2,4-dimethyl-3-pentanone (2.8 g, 0.025 mol) in 7 % yield (g.l.c.). ν_{max} 2960, 2930, 2870, 1460 cm^{-1}. m/e 154 (M^+, 5 %), 111 (37), 97 (5), 87 (11), 83 (37), 73 (15), 69 (100), 55 (50), 45 (19). δ_H (360 MHz; [$^2H_6$]dimethyl ether) 0.92 (6 H, d, J = 6.8 Hz), 1.00 (6 H, d, J = 6.8 Hz), 1.02 (6 H, d, J = 6.8 Hz), 2.27 (1 H, sept., J = 6.8 Hz), 2.83 (1 H, sept., J = 6.8 Hz), 2.65 (1 H, sept. of d, ^3J = 9.3 Hz, ^3J = 6.8 Hz), 4.95 (1 H, d, J = 9.3 Hz).

3-Isopropyl-2,4,5-trimethyl-3-hexene (8) was prepared according to Ref. 10 from 3-methyl-2-butanone (3.0 g, 0.035 mol) and 2,4-di-methyl-3-pentanone (4.0 g, 0.035 mol) in 27 % yield (g.l.c.). ν_{max} 2960, 2930, 2870. 1460 cm^{-1}. m/e 168 (M^+, 7 %), 125 (24), 97 (8), 83 (47), 69 (100), 55 (39). δ_H (360 MHz; [$^2H_6$]dimethyl ether) 0.97 (6 H, d, J = 7.0 Hz), 1.02 (6 H, d, J = 7.0 Hz), 1.10 (6 H, d, J = 7.0 Hz), 1.56 (3 H, s), 2.66 (1 H, sept., J = 7.0 Hz), 2.74 (1 H,

sept., $\underline{J}$ = 7.0 Hz), 3.01 (1 H, sept., $\underline{J}$ = 7.0 Hz). Attempts to prepare $\underset{\sim}{8}$ by the method with $TiCl_3$ and $LiAlH_4$ gave a by-product (1:1 compared to $\underset{\sim}{8}$) which could not be separated from $\underset{\sim}{8}$ even after repeated preparative g.l.c. treatments. The impurity was only observed on capillary gas chromatography and in the n.m.r. spectrum. It was identified through its n.m.r. spectrum as an isomer of $\underset{\sim}{8}$, 3-isopropyl--2,6-dimethyl-3-heptene.

^1H n.m.r. ($[^2H_8]$-toluene)



Assignments were verified by double resonance experiments. The vinylic proton couples with the methylene group, $^3\underline{J}$ = 7.0 Hz).

^1H N.m.r. spectra were recorded on a Nicolet 360 WB spectrometer. The samples were about 0.04 M in dimethyl-$\underline{d}_6$ ether and they were degassed by the high vacuum freeze-thaw technique before being sealed off. Me_4Si was used as internal reference. The temperature scale of the instrument was calibrated by the use of a methanol/$[^2H_6]$acetone sample, which in turn had been calibrated by the technique described in Ref. 11 using a JEOL MH-100 instrument.

N.O.e. difference experiments were run by automatic frequency alteration using the sequence; preirradiation (6 s), delay (50 ms),

pulse, and acquisition of one transient. After ca. 100 passes through the cycle the FID's were fourier transformed, identically phased and the spectra subtracted. The n.O.e. experiments were performed on degassed and sealed samples in [$^2H_6$]dimethyl ether.

Bandshape analysis was performed as previously described.[11] The free energy differences and the free energies of activation were calculated using eqs. (1) and (2) where p_A is the fractional molar population of conformer A.

$$\Delta G^o = 1.987 \cdot 10^{-3}\ T \ln \frac{p_A}{p_B} \text{ kcal mol}^{-1} \qquad (1)$$

$$\Delta G^{\ddagger} = 4.575 \cdot 10^{-3}\ T \left[10.319 + \log \frac{T}{k}\right] \text{kcal mol}^{-1} \qquad (2)$$

The calculations were performed on a PDP 11/34 computer with a GT 42 graphics terminal and a Printronix lineprinter/plotter of the Computer Graphics Laboratory for Organic Chemistry at the University of Lund.

Molecular mechanics calculations were performed using the MM2 or MMP2 programs developed by Allinger and coworkers, employing their 1977 force field.[12-14] The calculations were carried out with full relaxation techniques, and all input structures were optimized without symmetry or other constraints. The energy profiles for the rotation of the isopropyl and phenyl groups were obtained using the bond-drive techniques.

Results

Dynamic ^{1}H n.m.r. spectroscopy.- At ambient temperature the 360 MHz ^{1}H n.m.r. spectra of 1-8 display signals corresponding to fast conformational inversion on the n.m.r. timescale.

The spectrum of 1 remained unchanged down to -100 °C indicating the existence of one single conformation.

The spectrum of 2 exhibited selective broadening of the isopropyl methine septet at δ 2.56 below -20 °C. At -80 °C this signal resharpened as one single septet displaced ca. 0.1 ppm to higher field. No trace of a second septet coming from a minor conformer could be found, and the other signals remained sharp in the whole temperature interval.

The α-ethyl and α-isopropyl derivatives 3 and 4 behaved quite similar to 2 (Figure 1). In addition the lowfield methyl doublets (δ 1.28 for 3 and 1.30 for 4) broadened and resharpened in the same temperature interval, 0 to -70 °C. Attempts to identify signals from minor conformers by decoupling through irridiation at the methyl doublets failed. Apparently a very small population of a minor conformer, perhaps lessened by unfavourable entropies at low temperatures, is present for all three compounds 2-4. Bandshape analysis of the broadened isopropyl septets of 2-4, with the assumption that the chemical shift difference between major and minor conformations is between 0.5 and 2.2 ppm, indicate that the minor conformers constitute 0.5 to 3 % at the coalescence temperature.

β,β-Di-isopropyl-α-neopentylstyrene (5) displayed exchange-broadened spectra already at ambient temperature. Below -40 °C all signals from the isopropyl and neopentyl groups except the high-field isopropyl doublet decoalesced into two sets of signals corresponding

to two conformations of the isopropyl groups with the population ratio 65:35. The septets from the minor constituent were hidden under the solvent peak and were found by irradiation at several frequencies with observation of the decoupling of their corresponding doublets.

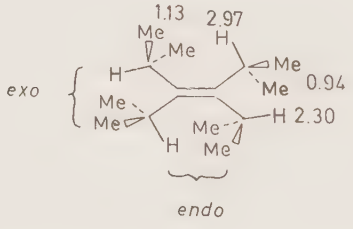
Below -70 °C a second process appeared as a selective decoalescence of one isopropyl doublet (δ 0.86) and the methylene signal of the minor conformation. The detailed shape of these signals at -125 °C, at the slow exchange limit, was not resolved due to broad spectra probably caused by a third process becoming slow on the n.m.r. timescale. The barrier was estimated to 9.4 ± 0.4 kcal mol^{-1} at -90 °C.

The spectrum of β,β-di-isopropyl-α-t-butylstyrene (6) displayed changes of the isopropyl signals in the temperature range -20 to -105 °C while the t-butyl signal remained essentially unchanged. At -110 °C two sets of signals with the intensity ratio 9:91 appeared (Figure 2). The septets of the minor conformation were just about recognizable but appeared clearly by decoupling through irradiation of the appropriate doublets.

No sign of changes was observed in the spectrum of 3-isopropyl-2,5-dimethyl-3-hexene (7) down to -100 °C, while 3-isopropyl-2,4,5-trimethyl-3-hexene (8) gave rise to decoalescence of all signals. At -70 °C two sets of signals of the relative intensities 73:27 were obtained (Figure 3). The temperature dependence of the equilibrium was followed in the range -55 to -125 °C and gave ΔH^{o} = 0.49 ± 0.10 kcal mol^{-1} and ΔS^{o} = -0.50 ± 0.05 cal mol^{-1} K^{-1}.

A summary of the d.n.m.r. results and the derived energy parameters is found in Table 1.

Conformational and n.m.r. assignments.- The conformational attributions in Table 1 are based on chemical shift considerations, double resonance and n.O.e. difference techniques as well as on results of the MM calculations (vide infra). The relative n.m.r. chemical shifts of the isopropyl methyl and methine signals are primarily determined by the anisotropy of the double bond and the phenyl group and by van der Waals' shifts of proximate alkyl groups. Two idealized positions can be visualized for each of the methyl and methine groups, here called endo and exo.



The difference in chemical shift between endo and exo positions for the methyl and methine protons, due to the anisotropy of the double bond, may be illustrated by tetra-isopropylethylene,[15] for which the proposed assignments are based upon the conclusions from this work. The anisotropic shielding effects of the phenyl group are strongly depending upon the twist angle between this group and the double bond. However, chemical shift considerations alone do not allow for conclusive attributions, and we had to seek additional evidence. First, the combination of couples of doublets and septets for all isopropyl groups in all conformations was established by decoupling. A powerful technique, which has become available by modern pulse n.m.r. instrumentation, is the n.O.e. difference spectroscopy.[16]

This was applied to the compounds 1-8 both at room temperature and at temperatures where the exchange rate is slow, below -75 °C in most cases.

In compound 1 only one rotamer is observed, which we allocated to conformation A. A n.O.e. enhancement of the vinylic proton signal was caused by preirradiation of the doublet at δ 1.14 establishing the proximity between these groups.

There is a striking similarity between 2, 3, and 4 both in dynamic behaviour and in chemical shifts of the β-isopropyl groups. Conformational assignment of the strongly dominating rotamer was supported by the following n.O.e. experiments. Partial saturation of the methyl signal at δ 1.96 of 2 led to enhancement of the doublet at δ 1.27 and vice versa. In 3 preirradiation of the doublet at δ 0.86 caused enhancement of the septet at δ 2.50 and in 4 preirradiation of the doublet at δ 1.29 gave enhancement of the septet at δ 3.23. The latter septet was identified by selective deuteration of the methine proton of the isopropyl geminal to the phenyl group. All these experiments point at A as the dominant rotamer. Compounds 2, 3, and 4 have very similar chemical shifts of the β-isopropyl groups with the exception that the endo proton cis to the phenyl in 4 appears at somewhat higher field. This upfield shift could be semi--quantitatively reproduced by screening constant calculations[17] using the geometries from the MM calculations according to which this proton is situated in a more shielding position than the corresponding protons in 2 and 3. More striking is the deviation of the chemical shifts of the cis-isopropyl group in 1. This is explained by a much smaller angle around the phenyl-olefin bond in 1, placing these protons in the deshielding region of the phenyl anisotropy. A more

planar arrangement in 1 is found in MM calculations and also supported by u.v. spectra (see below).

The α-neopentyl derivative, 5, exists in at least two rotamers. Preirradiation of the doublet, at δ 1.29, of the major constituent enhanced the singlet at δ 2.54 of the methylene group. Furthermore, the chemical shifts of the isopropyl protons in the major constituent are quite similar to the corresponding values in 2-4. The shifts of the methylene protons experience the expected van der Waals' shift in rotamer A whereas the t-butyl group shifts in the opposite direction, probably because of a change of conformation with respect to the phenyl group.

The attribution of the major constituent of 6 was confirmed by n.O.e. enhancement of the septet at δ 3.42 on preirradiation of the t-butyl signal at δ 1.02. For the attribution of the minor constituent to rotamer C we had to resort to MM calculations, but the chemical shifts are also in best agreement with this conformation. Thus, the shift of the trans-isopropyl methine proton is hardly compatible with any other conformation of this isopropyl group.

In 7 a relatively large three-bond coupling of 9.3 Hz between the olefinic proton and the geminal isopropyl methine proton assigns this isopropyl group. No significant n.O.e. effects were obtained, and the assignment of the only observed conformation to rotamer B was based on MM calculations and chemical shift comparisons.

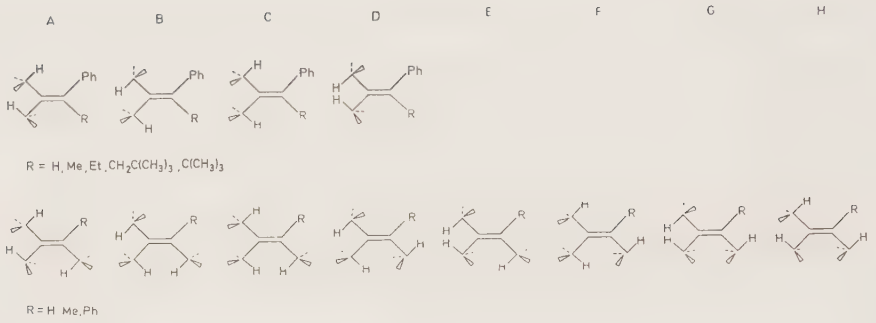
The resonance of the isopropyl group geminal to the methyl group of 8 is easily identified, since this group maintains the same conformation in the two possible rotamers A and B, and thus a very small splitting is observed. Furthermore, a selective n.O.e. enhancement of the doublet at δ 0.94 was observed on preirradiation of the methyl

resonance at δ 1.49. In order to decide among the alternative rotamers A and B we use the following arguments. First, the chemical shifts of the C=C-CH_3 group in the two conformations are best understood by a van der Waals' effect caused by the cis-isopropyl methyls in a conformation as in B. Second, preirridiation of the methyl group at δ 1.49 led to enhancement of only one septet, the one at δ 2.84.

Molecular mechanics calculations.- In order to treat the conformational situation in the present set of molecules, a computational procedure which includes the conjugation in the π-electron system must be applied. We have used the MMP2 force field,[13] in which a π-electron selfconsistent-field calculation generates the necessary force constants for stretching and torsion for the bonds connecting the π-system atoms. A crucial parameter in the calculations is the torsional angle about the phenyl-ethylene bond. Fortunately, the MMP2 force-field satisfactorily reproduces the planarity of styrene as well as the torsional barrier.[18]

Throughout the series 1-8 the calculations predict four types of minima when mapping the energy as a function of the two dihedral angles defining the conformations of the geminal isopropyl groups, giving rise to the rotamers A-D. In 4, 7, and 8 another four rotamers, E-H, are obtained due to the two possible conformations of the third isopropyl group (Scheme 3). The calculated energies of all stable rotamers are found in Table 2 and geometrical parameters of the two low-energy forms of each compound are given in Table 3.

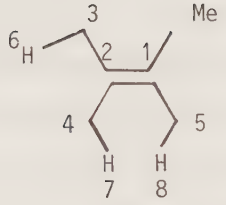
The calculated dihedral angles at the phenyl-ethylene bond (2-1-9-10) are mostly close to 90°. The largest deviation is found for 1 in which the absence of an α-substituent enables a reduction of



Scheme 3

the dihedral angle to 52°. In the two α-primary-alkyl derivatives 3 and 5 the ethyl and neopentyl groups project towards one side of the ethylene plane, thus introducing an unsymmetrical buttressing of the phenyl group leading to a reduction of the angle to 78° and 70°, respectively. The geminal isopropyl groups deviate only slightly from the ideal bisected conformation in the gear-meshed rotamers A and B, somewhat more in C and D. These calculated rotamer geometries are in harmony with the chemical shift features discussed above. The calculated structures and chemical shift assignments are shown in Figure 4.

The conformational change of the isopropyl groups between two gear-meshed conformations may proceed through a stepwise mechanism, where the isopropyl groups rotate one at a time over intermediates such as C or E, or through a correlated rotation over a single transition state. By use of the incremental group driving technique, one might get information to aid a decision among these alternatives. Such calculations were performed on 8 by driving the torsional angles C(1)-C(2)-C(3)-H(6), C(1)-C(2)-C(4)-H(7), and C(2)-C(1)-C(5)-H(8).



The results are given in Figure 5. The favoured pathway is an uncorrelated rearrangement over the rotamer E with a calculated barrier of 11.0 kcal mol^{-1} (B → A). Any correlated rotation of the isopropyl groups (two or three) requires barriers which are at least twice as high as the uncorrelated mechanism.

The barrier to rotation around the phenyl-ethylene bond was studied for 1 and 2 (Figure 6). The calculations were performed on rotamers A in both cases, corresponding to the experimental minimum energy conformations. 1 has a calculated angle between the ring and ethylene planes of 52° and two barriers corresponding to the planar and 90° twisted arrangements of 4.7 and 0.8 kcal mol^{-1}, respectively. In 2 there is a rather shallow minimum around the 90° twisted conformation and a barrier of 12.6 kcal mol^{-1} for passage of the planar form.

Ultraviolet spectroscopy.- The u.v. spectra of the styrenes 1-6 in hexane are given in Table 4. The most interesting band, the K-band, appears at 248 nm in styrene. The hypsochromic shifts of this band correlate well with the calculated twist angles about the phenyl-olefin bond, 1 and 5 being the only structures for which the angle significantly deviates from 90°.

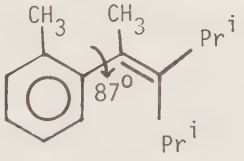
Discussion

The conformation of two geminal isopropyl groups has been extensively studied in N,N-di-isopropylamides, -thioamides and one selenoamide.[6,19-21] Rotamers corresponding to A and B are observed in the majority of the cases, and the equilibrium between them, and the barrier separating them are determined by the effective sizes of X and Y (Scheme 1). When both X and Y are large, as for X = CH_3Se and Y = Se or X = CH_2Ph and Y = S, rotamer c appears, while d has not been found so far. However, d is predicted by molecular mechanics calculations in cases of small flanking substituents, and it has been observed in cases with vicinal isopropyl groups.[22]

The general pattern observed for the conformation of geminal isopropyl groups in amides and thioamides is also found in the series 1-8, i.e. the "gear-meshed" rotamers a and b are preferred. Only for 6, and, possibly 5, rotamer c is appreciably populated. The systems 4, 7, and 8 bear vicinal isopropyl groups, and for this configuration the conformation in which the isopropyl groups present their methine protons towards each other turns out to be at least as favourable as the "gear-meshed" ones. Such a conformation is governed by the eclipsing of the double bond by both methine protons and is also found for simple analogues, such as cis-2-butene.[23]

The most striking aspect of the results summarized in Table 1 is the reluctance of the systems 1-6 to take up conformations in which the cis-isopropyl group exposes its bulkier face, the methyl groups, towards the phenyl group. Using the populations of the rotamers as a measure of the effective size in these systems the following order is obtained. $H \ll CH(CH_3)_2 < CH_3 \leq C_2H_5 < CH_2C(CH_3)_3 <$

< Ph < $C(CH_3)_3$. In energy terms, given by the ΔG^o values in Table 1, the phenyl-methyl difference is at least 1.3 kcal mol^{-1} and the phenyl-neopentyl difference at least 0.27 kcal mol^{-1}. Very recently, several papers have appeared treating the steric interactions between the phenyl group and alkyl groups in various systems.[24-28] It turns out, that whenever the phenyl ring can expose its planar face towards a flanking methyl without interfering with other substituents, or with the framework, it behaves as if it were "smaller" than or of about the same size as the methyl group, in salient contrast to our findings. Must we conclude then, that the phenyl group is considerably more coplanar with the ethylene plane than was concluded from both experimental and computational considerations in this work? The experimental evidence, including n.m.r. chemical shifts and u.v. spectra, is a rather coarse measure of the phenyl-olefin angles. Further evidence is found in a comparison of the behaviour of 2-4 with that of β,β-di-isopropyl-α,2-dimethylstyrene (9), which is strongly twisted in the ground state and has a high torsional barrier around the phenyl-olefin bond.[5] 9 has n.m.r. and u.v. spectra which are very similar to those of 2-4.



$\Delta G^{\ddagger}_{340}$ = 25.4 kcal mol^{-1}

9

How reliable, then, are the MM calculations on this point? The energy profile for rotation around the phenyl-ethylene bond, and

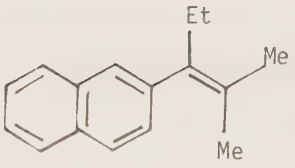
particularly, the shape of the curves around the minima, may give information about the reliability of the calculated phenyl-ethylene dihedral angles. As seen in Figure 6, a change of the dihedral angle in 2 by ca. 30^{o} from the minimum energy value (86^{o}) raises the energy by 1 kcal mol^{-1}. A minor deficiency in the force field may thus cause erroneous values of these dihedral angles. Furthermore, since the potential energy surface around the minimum certainly is much steeper in rotamer B than in A, due to the stronger interaction between the phenyl ring and the cis-isopropyl group, torsional liberation of the phenyl group may entropically favour rotamer A.

Thus, although deviation from orthogonality and torsional liberation may contribute to increase the apparent size if the phenyl group, we believe that the major origin is to be sought in the specific interactions between the isopropyl group and the phenyl group. When polyhedral substituents interact with each other, strain accommodation takes place mainly by rotation of the polyhedral groups, so as to find a conformation of comparably low energy (gear effect).[6] In this work, that is manifested by the interaction between the β-isopropyl groups. In the isopropyl-phenyl interaction of the styrenes there is no such effective relaxation mechanism, and thus the bulkier dimethyl side of the isopropyl group and the face of the phenyl group experience considerable strain when they interact in a cis-vicinal arrangement. This illustrates that important energy differences can appear depending upon how conveniently various groups can get on together sterically. In a recent gas chromatographic study it was shown that alkyl-phenyl interactions depend upon the shape of the alkyl group.[29] Furthermore, the geometry of the framework and the substitution pattern also have a profound influence on the interaction between phenyl and alkyl

groups. Thus, the aromatic ring face presents a very small hindrance to geminal isopropyl and neopentyl groups in N-alkyl(thio)anilides[28] in agreement with our finding for 4, in which the isopropyl group geminal to the phenyl group prefers a conformation in which it turns its bulkier face toward the phenyl.

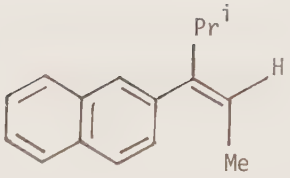
Comparison of the data in Table 1 with those of Table 2 shows that only four out of eight entries agree as to the most stable rotamer. A closer look reveals that in 2-5 the calculations tend to unjustifiedly favour the conformation, in which the cis-isopropyl group exposes its bulkier face, the methyl groups, towards the phenyl group, by 0.5-1.5 kcal mol^{-1}. Although a minor part of this discrepancy can be ascribed to effects such as differential solvation or to an entropy term, we believe that the major role is to be found in some inadequacy in the force field. One possibility is that the standard MMP2 force field underestimates the steric requirements of the faces of the benzene ring. However, the rather poor agreement between experimental ΔH^{o} (0.5 kcal mol^{-1}) and calculated ΔE (-0.13 kcal mol^{-1}) values for 8 is an indication that other factors may also contribute.

The calculated barriers to rotation of the phenyl group in 1 and 2, 4.7 and 12.6 kcal mol^{-1}, respectively, conform with experimental barriers in β-naphthylethylenes, such as 9-12,[3] but a closer comparison is not possible, since the barrier is extremely sensitive to the substitution pattern in α and β positions.[2,3] However, methyl substitution in the ortho position of 2 renders the molecule chiral and thus the barrier experimentally accessible, $\Delta H^{\ddagger}$ = 18.9 ± 1.0 kcal mol^{-1}, a value somewhat lower than the calculated one, 21.4 kcal mol^{-1}.[5]



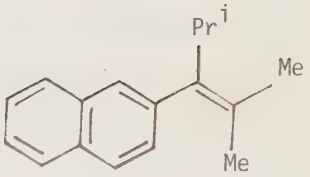
10

$\Delta G^{\ddagger}$ = 6.6 kcal mol^{-1}



11

$\Delta G^{\ddagger}$ = 5.2 kcal mol^{-1}



12

$\Delta G^{\ddagger}$ = 12.9 kcal mol^{-1}

The barriers to interchange of the isopropyl groups fall in the rather narrow range of 10.5-12.2 kcal mol^{-1}. The highest barrier (8, 12.2 kcal mol^{-1}) is obtained for the conceptually less strained molecule and the lowest barrier (6, 10.5 kcal mol^{-1}) for the most strained one. This is a typical "ground-state effect", i.e. a lower ground-state strain in 8 is not compensated for by a higher transition-state strain in 6. According to the calculations on 8, these processes proceed through stepwise rotation of the isopropyl groups via rotamer E, in agreement with several earlier findings.[6,19-21,30,31] The calculated barrier, 11.0 kcal mol^{-1}, is ca. 1 kcal mol^{-1} lower than the experimental value, as frequently observed in similar calculations.[31]

Finally, the low temperature features of the n.m.r. spectrum of 5 deserve some comment. As was mentioned above, signs of further exchange processes were observed in the temperature range -70 to -135 °C, which could not be satisfactorily analyzed due to unresolved spectra. We envisage two possible processes to account for the observations; the rotation of the neopentyl group and the rotation of the isopropyl group cis to the phenyl. The latter alternative implies that the first decoalescence be ascribed the freezing of the rotation of only one isopropyl group, the one trans to the phenyl,

the cis-isopropyl group still rotating fast. Actually, this alternative is not unreasonable, considering the calculated rotamer energies of 5 (Table 2), and that the stability of rotamer B seems to be exaggerated by ca. 1 kcal mol^{-1} in the MM calculation.

In summary, conformational analysis of a series of α-alkyl--β,β-di-isopropylstyrenes leads to the following conclusions: (i) the phenyl group is twisted ca. 70-90° out of the ethylene plane and (ii) the conformational populations of the geminal isopropyl groups indicate that the effective steric size of the phenyl group is larger than those of methyl, ethyl, isopropyl and neopentyl groups, but smaller than that of the t-butyl group.

This unexpectedly large apparent size of the phenyl group, in view of the large twist angle, is rationalized by reluctance of a phenyl group and the bulkier face of the isopropyl group to tolerate each other sterically, when placed cis-vicinal to each other.

Molecular mechanics calculations fail to reproduce the experimentally determined conformational populations and seem to underestimate the steric requirements of the phenyl group in cis--vicinal interactions with the methyl groups of an isopropyl group by ca. 1 kcal mol^{-1}. The calculations reproduce barriers to rotation of the isopropyl and phenyl groups to within ca. ± 10 % of $\Delta G^{\ddagger}$ (or $\Delta H^{\ddagger}$) values.

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Table 1. Fractional populations, ΔG^{o} and $\Delta G^{\ddagger}$ (major → minor) for compounds 1-8

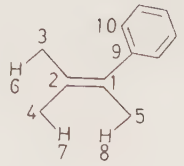
Compd.	Major conf., %		Minor conf., %		ΔG^{o} [a]	T [b]	$\Delta G^{\ddagger}$ [a]	T [b]
1	A	≥ 99			> 1.5			
2	A	97-99.5	(B)	0.5-3	≥ 1.3 ≤ 2.2	225	11.3	225
3	A	97-99.5	(B)	0.5-3	≥ 1.3 ≤ 2.2	225	11.1	225
4	A	97-99.5	(B)	0.5-3	≥ 1.3 ≤ 2.2	253	12.0	253
5	A	65	B	35	0.27 ± 0.05	218	11.5	240
6	B	91	C	9	0.75 ± 0.10	164	10.5	210
7	B	≥ 99			≥ 1.5			
8	A	73	B	27	0.60 ± 0.10 [c]	203	12.2	234

[a] ± Kcal mol^{-1}. [b] ± K. [c] ΔH^{o} = 0.49 ± 0.10, ΔS^{o} = -0.50 ± 0.05.

Table 2. Relative calculated energies of the rotamers A-H in kcal mol^{-1}

Compd.	A	B	C	D	E	F	G	H
1	0.00	2.91	3.51	2.54				
2	0.19	0.00	1.36	2.35				
3	0.23	0.00	1.83	2.79				
4	0.00	0.49	1.29	2.65	3.43	4.03	10.91	8.14
5	0.21	0.00	0.74	3.48				
6	5.76	0.00	1.06	9.72				
7	0.92	0.00	2.59	1.16	1.81	5.09	8.07	8.17
8	0.13	0.00	1.49	1.69	2.78	3.96	10.55	8.58

Table 3. Selected calculated structural parameters



Compd.	Conformation	2-1-9-10 [a]	1-2-3-6 [a]	1-2-4-7 [a]	2-1-5-8 [a]	1-2 [b]	2-1-9 [c]
1	A	51.9	2.0	176.3	–	1.349	126.8
	D	71.0	144.3	169.3	–	1.346	127.2
2	A	86.4	6.6	167.2	–	1.352	120.4
	B	85.1	176.4	2.6	–	1.352	124.0
3	A	77.9	4.7	172.0	–	1.353	120.2
	B	89.5	174.0	4.4	–	1.353	123.4
4	A	88.2	0.7	178.8	2.8	1.353	119.0
	B	89.5	168.6	8.3	40.2	1.356	121.9
5	A	69.7	2.7	176.1	–	1.356	119.7
	B	76.7	159.5	15.0	–	1.356	122.2
6	B	87.2	179.9	0.1	–	1.358	119.3
	C	88.0	20.6	13.8	–	1.361	117.4

Table 3. Continued.

7	B	–	180.0	0.1	0.2	1.347	–
	A	–	0.1	179.9	0.3	1.348	–
8	A	–	10.1	172.0	7.2	1.356	–
	B	–	170.0	11.4	30.4	1.357	–

[a] Torsional angle, deg. [b] Bond length, Å. [c] Bond angle, deg.

Table 4. U.v. spectra in hexane.

Compound	λ_1 [a] (ε_1)	λ_2 [a] (ε_2)	λ_3 [a] (ε_3)
Benzene [b]	203.5 (7400)	254 (204)	–
Styrene [c]	248 (14000)	282 (750)	291 (500)
1	242 (27800)	–	–
2	231 (5400)	–	–
3	230 (6100)	–	–
4	223 (S)	254 (3000)	
5	246 (18900)	–	–
6	218 (S)	262 (4400)	–

[a] nm. [b] In hexane. [c] In ethanol.

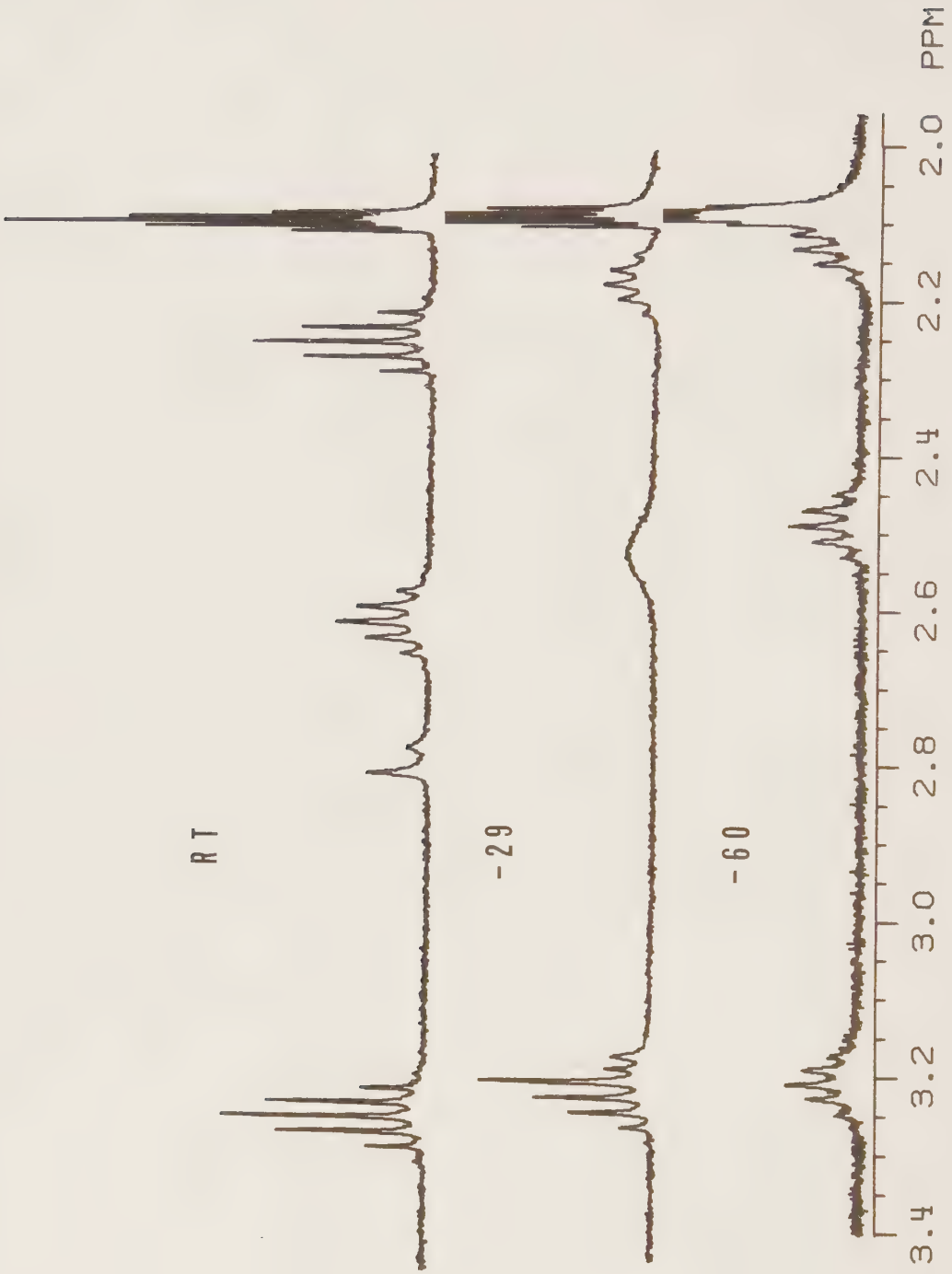


Figure 1. 360 MHz ^{1}H n.m.r. spectrum of $\underset{\sim}{4}$ in [$^{2}H_{6}$]-acetone at different temperatures showing the isopropyl-septet region. Peaks at δ 2.8 at room temperature and amidts the septet at δ 3.2 at -29 ^{o}C are impurities.

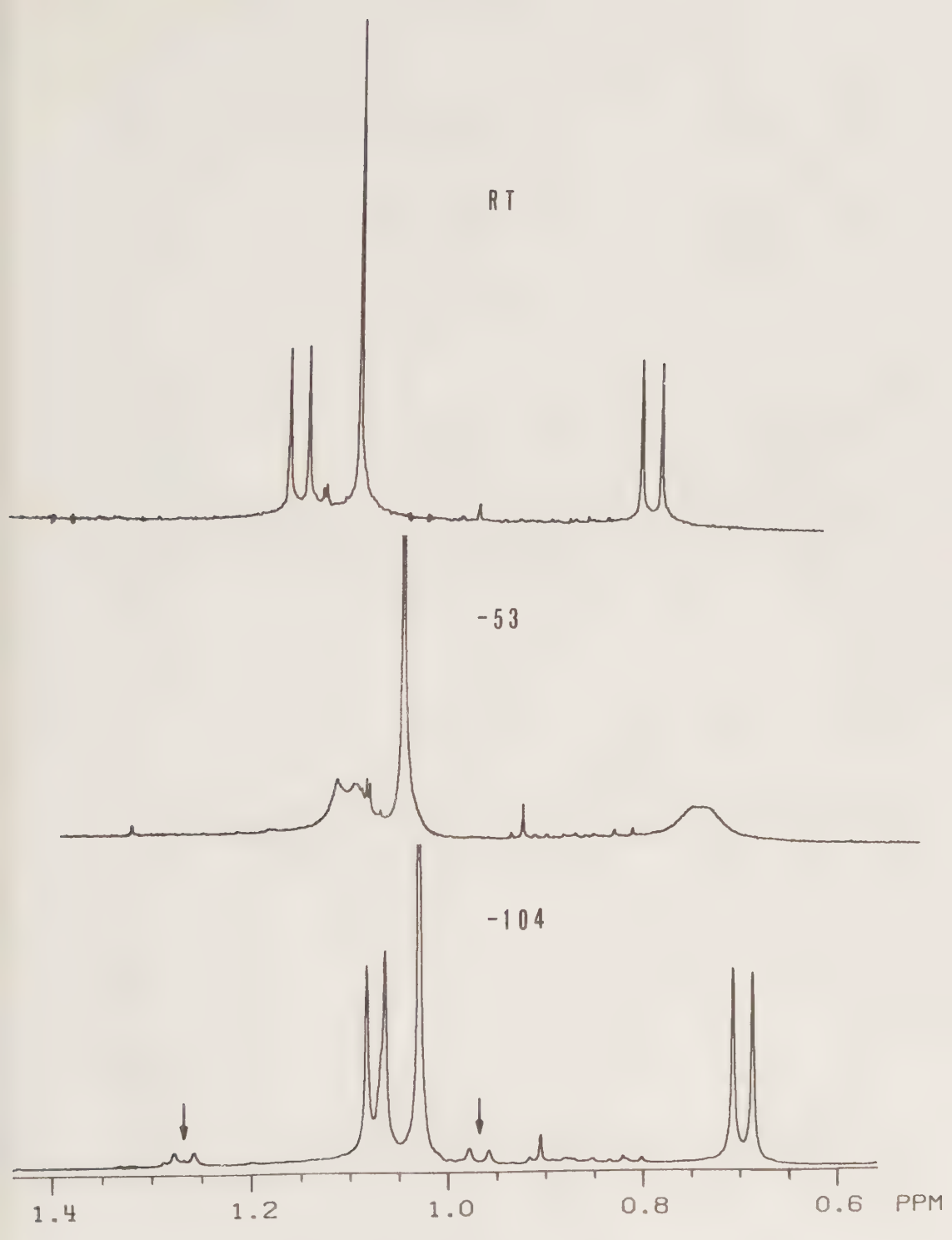


Figure 2. 360 MHz ^{1}H n.m.r. spectrum of 6 in [$^{2}H_{6}$]-dimethyl ether at various temperatures showing the isopropyl-methyl region and the Bu^{t}-signal. Arrows indicate the doublets from the minor conformation.

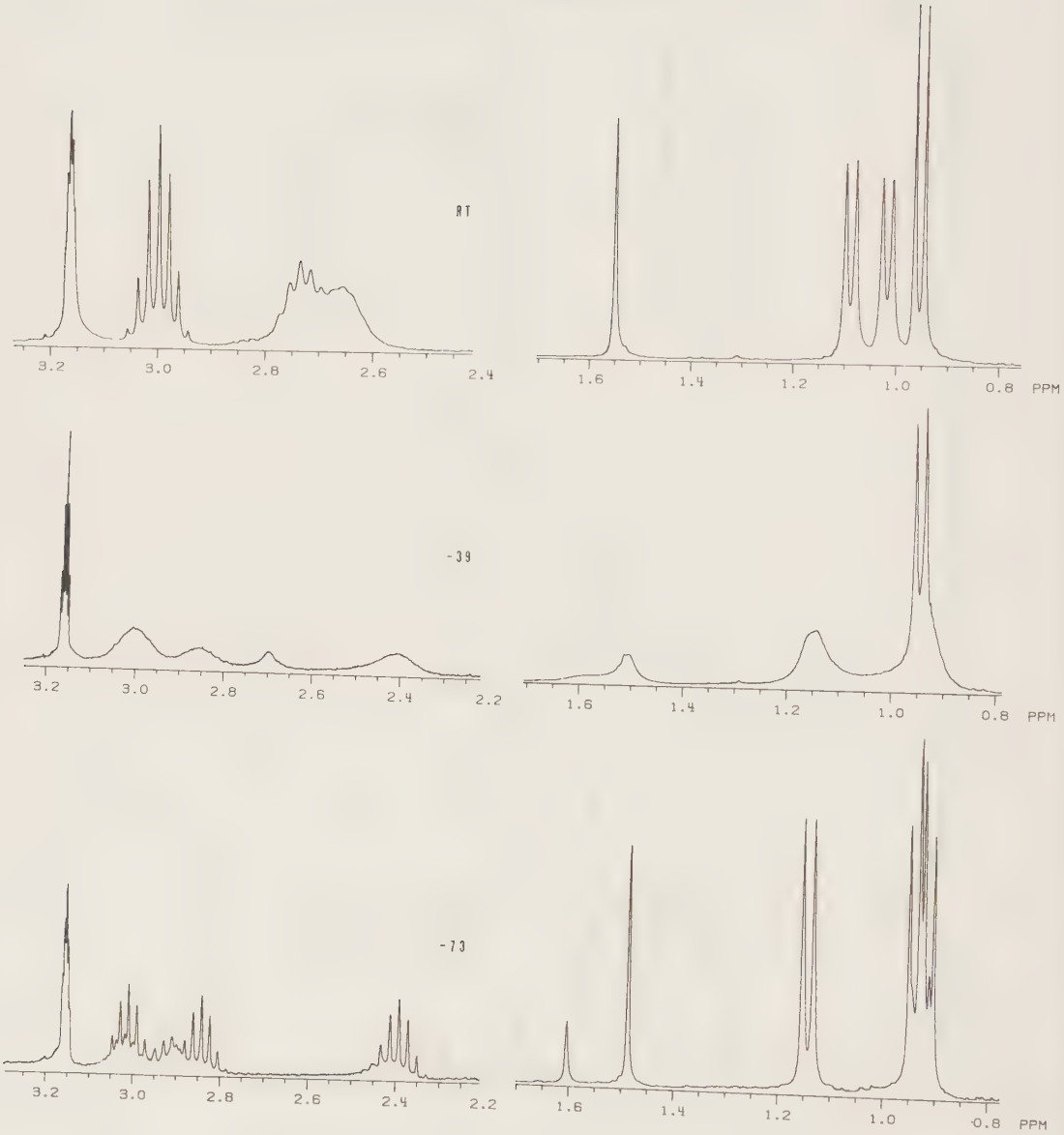


Figure 3. 360 MHz ^{1}H n.m.r. spectrum of 8 in $[^{2}H_{6}]$-dimethyl ether at various temperatures. Solvent peak at δ 3.15.

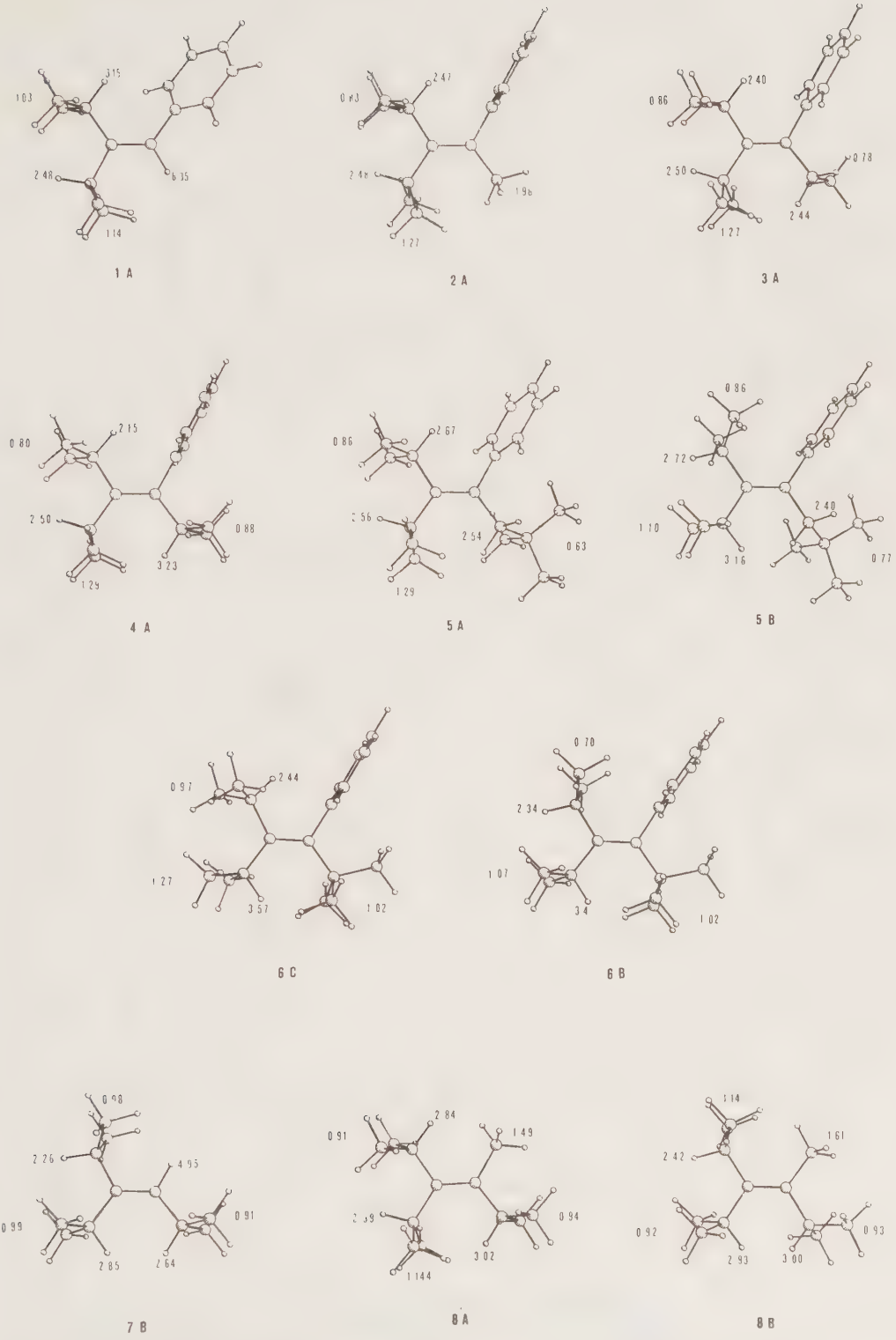


Figure 4. Structures of all conformers of 1-8, that are appreciably populated, calculated by the MM2 or MMP2 force fields. Inserted values are chemical shifts at low temperature in [$^2H_6$]-dimethyl ether for all signals exept those from the aromatic protons.

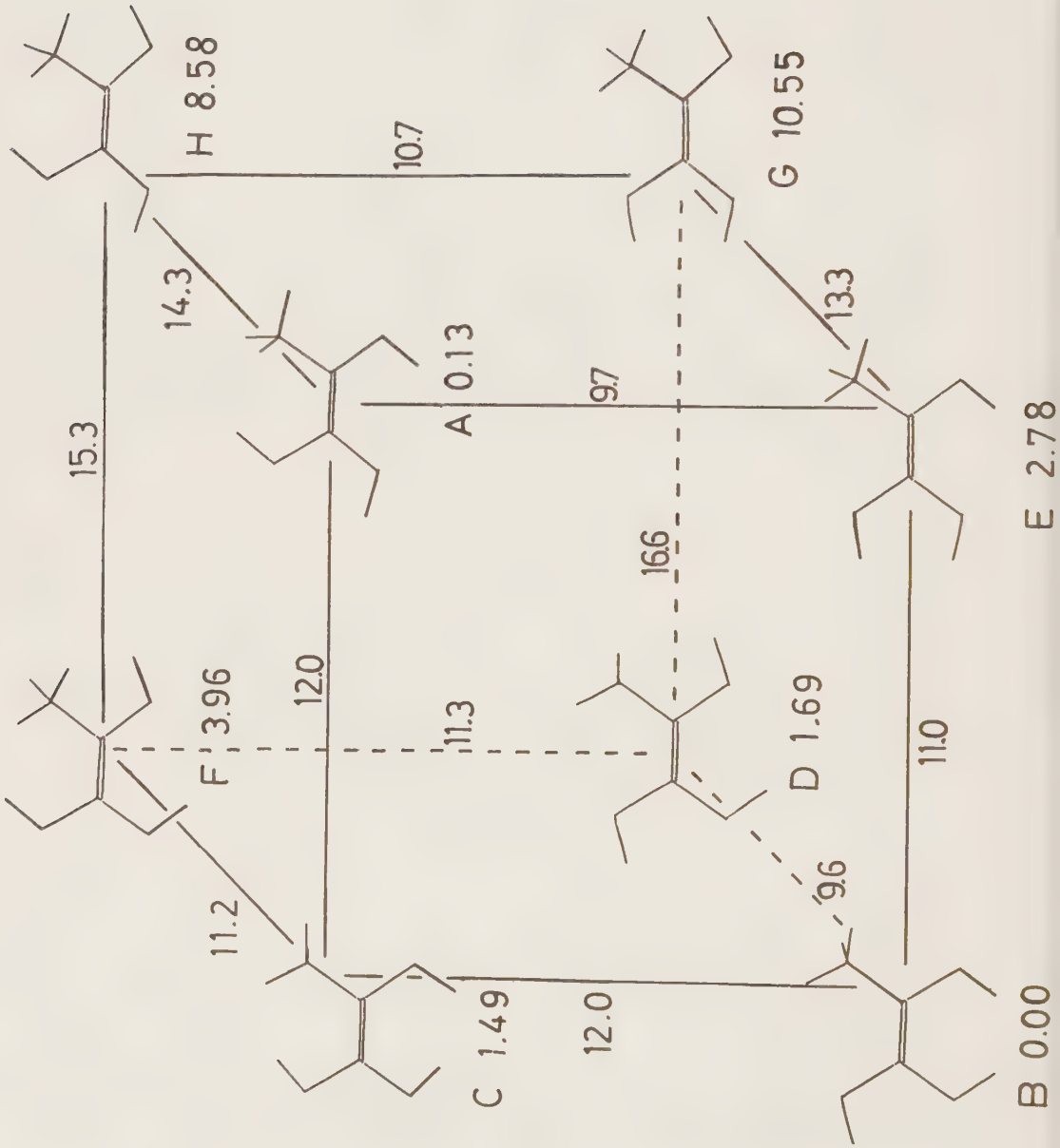


Figure 5. Rearrangement graph for 8 showing the calculated relative energies of the conformers and the barriers to rotation from the more stable to the less stable rotamer.

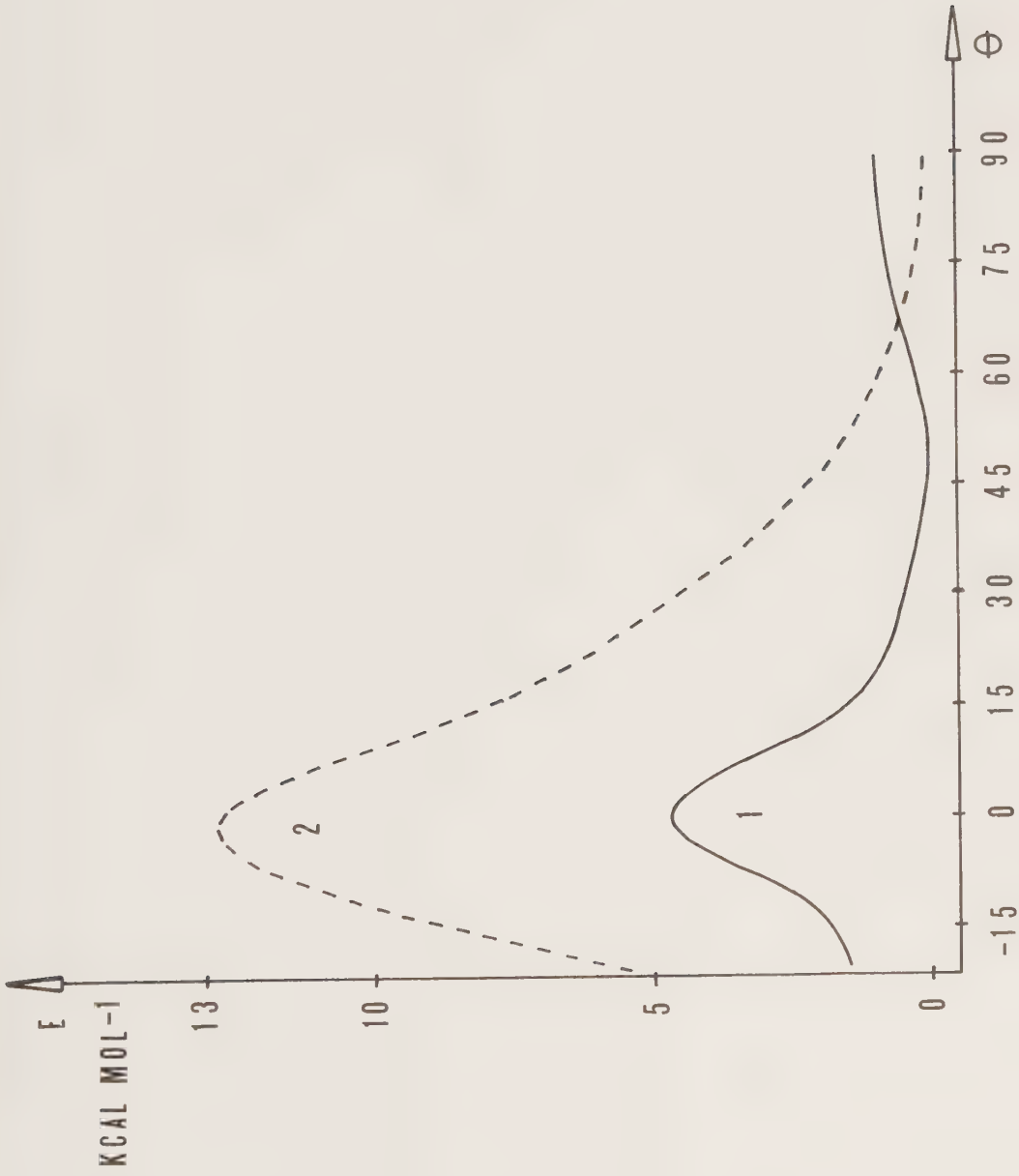


Figure 6. Relative steric energy of 1 and 2 as a function of the torsional angle between the benzene and ethylene planes calculated by the MMP2 force field.

PAPER III

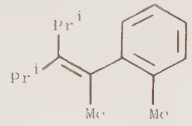
Enantiomer Resolution, and Stereodynamic and Chiroptical Properties of β,β-Di-isopropyl-α,2-dimethylstyrene†

J. Chem. Research (S), 1984, 208–209†

INGRID PETTERSSON and ULF BERG*

Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 740, S-220 07 Lund, Sweden

We report a stereochemical study of β,β-di-isopropyl-α,2-dimethylstyrene (1); techniques include dynamic ^{1}H n.m.r. spectroscopy, chromatographic enantiomer resolution on triacetylcellulose, thermal racemization, c.d. spectroscopy, and molecular mechanics calculations.



(1)

While styrene is a planar molecule with a barrier of *ca.* 3 kcal mol^{-1}‡ to rotation about the phenyl-to-olefin bond,[1] derivatives of styrene substituted in the α and β positions are twisted with a barrier towards torsion through a planar transition state.[2,3] When such a twisted styrene is unsymmetrically substituted in the *ortho* positions, the molecule is chiral, and if the barrier is sufficiently high, optical resolution is possible.[4] The torsional barrier, which is due to steric interactions in the planar state, is remarkably sensitive to the substitution pattern, as has recently been reported for 1- and 2-alkenylnaphthalenes.[2,3]

The ^{1}H n.m.r. spectrum of (1) shows geminal diastereotopism[5] of the high-field isopropyl methyl groups (δ = 0.82 and 0.89) as expected when the rotation around the aryl–ethylene bond is slow (Figure 1a). The pairs of doublets show selective broadening from +180 °C (100 MHz in hexachloroacetone), and bandshape analysis at 192.3 °C gives $k_{rot} = 2.5 \pm 1.0$ s^{-1} ($\Delta G^{\neq} = 26.8 \pm 0.3$ kcal mol^{-1}). This suggests that it should be possible to resolve (1) into stable enantiomers.

The n.m.r. spectrum also exhibits temperature dependence at lower temperatures. At −40 °C a selective broadening of the low-field isopropyl septet (δ 2.60) was observed and at still lower temperatures the septet sharpened again, displaced *ca.* 0.09 p.p.m. to higher field. No significant change of the other signals was observed. This phenomenon was interpreted, based on experiences from a broader dynamic n.m.r. investigation of α-substituted β,β-di-isopropylstyrenes currently in completion,[6] as the conformational change of the isopropyl groups between two 'geared' conformations with a strong preference for one constituent (Figure 2). The major constituent was assigned the conformation (1a), on the basis of chemical shift considerations and decoupling and nuclear Overhauser enhancement (n.O.e.) experiments. Bandshape analysis at −40 °C, with the assumption that the chemical shift difference between the two sites is ≤2 p.p.m., provides a maximum population of the minor constituent of 3% ($\Delta G^0 \geq 1.3$ kcal mol^{-1}) and a barrier of 9.8 ± 0.3 kcal mol^{-1} (minor → major) was estimated.

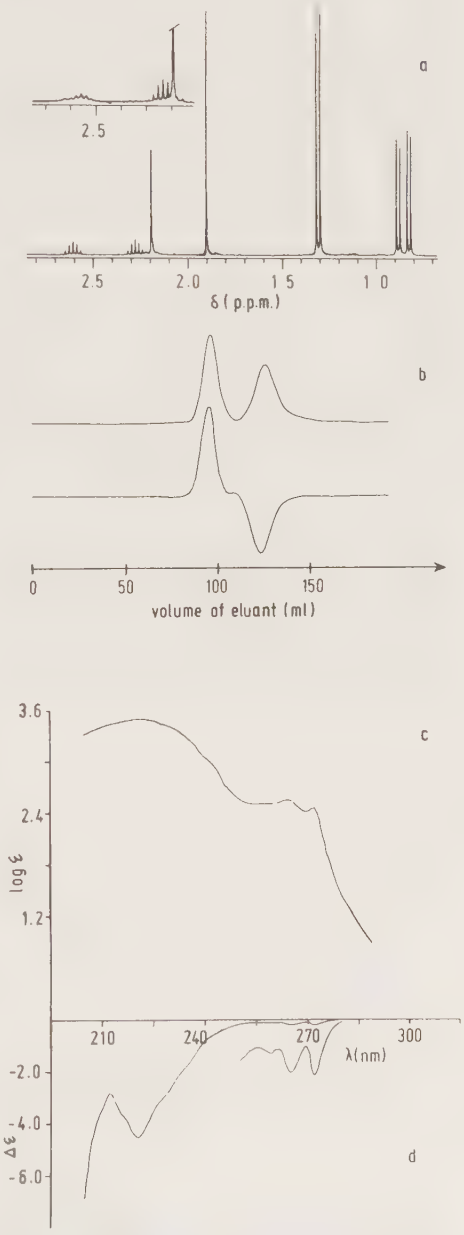


Figure 1 (a) 360 MHz n.m.r. spectrum of (1) in $(CD)_2O$; inserted trace at −50 °C. (b) U.v. (upper trace) and polarimetric detection of chromatographic resolution of (1) on triacetylcellulose. (c) U.v. and (d) c.d. spectrum of (−)-(1) in hexane.

*To receive any correspondence.

†This is a Short Paper as defined in the Instructions for Authors [*J. Chem. Research (S)*, 1984, Issue 1, p. iv]; there is therefore no corresponding material in *J. Chem. Research (M)*.

‡1 cal = 4.184 J.

Swollen, microcrystalline triacetylcellulose has earlier proven useful for the resolution of racemates including stable atropisomers.[7,8] Chromatography of racemic (1) led to baseline separation (Figure 1b), which was easily developed into semipreparative enrichment of essentially optically pure enantiomers; $[\alpha]_{365}^{20} = 113 \pm 5°$ (*c*, 0.23 in EtOH).

Thermal racemization of (1) in propanol at five temperatures (50–75 °C) resulted in the following activation parameters for the rotational barrier: $\Delta G^{\neq}_{340} = 25.4 \pm 0.1$ kcal mol^{-1}, $\Delta H^{\neq} = 18.9 \pm 1.0$ kcal mol^{-1}, and $\Delta S^{\neq} = -19.0 \pm 3.0$ cal mol^{-1} K^{-1}. These results are reasonably compatible with the barrier determined by dynamic n.m.r. spectroscopy reported above, if the difference in temperature is taken into account. The large negative entropy of activation deserves some comment. Rather negative $\Delta S^{\neq}$ values (*ca.* −10 to −20 cal mol^{-1} K^{-1}) have been observed for racemization of similar compounds, *i.e.* biphenyls and binaphthyls.[9,10] These negative values are probably governed by changes in the vibrational frequencies on going to the rather strained transition state. In (1), a negative contribution may also result from partial loss of rotational freedom of the methyl groups in the transition state.

The c.d. and u.v. spectra exhibit two bands, one at 266 nm of low intensity and with vibrational fine structure, and a broad band centred at 220 nm (Figures 1c and d). The spectrum is more similar to the sum of those of the aryl and alkene groups than to the spectrum of styrene, indicating an appreciable twist angle giving rise to isolated chromophores. The determination of the absolute configuration by theoretical treatment of the Cotton effects was not considered feasible, as the signs and magnitudes of the rotational strength are very sensitive to the dihedral angle at the pivot bond.

Molecular mechanics calculations give two stable conformers of low energy with geared isopropyl groups and differing in energy by 0.15 kcal mol^{-1}, significantly less than the experimental value (≥1.3 kcal mol^{-1}) (Figure 2). The angle between the ring and the ethylene planes is 87° in both conformers. The calculated torsional barrier is 21.4 kcal mol^{-1} with the ring methyl passing the α-methyl of conformer (1a) in the low-energy pathway.

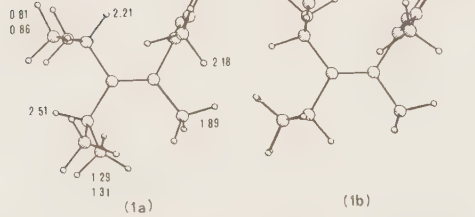


Figure 2 The two low-energy conformers of (1) calculated by the MMP2 force-field. Inserted values are n.m.r. chemical shifts at −80 °C.

In this study the combination of several experimental and theoretical methods provides a detailed picture of the dynamic behaviour of a stereochemically versatile molecule. The rotational barrier around the aryl–ethylene bond is comparable to that of similarly substituted alkenylnaphthalenes.[2,3] The isopropyl groups prefer to turn their bulkier face[11] towards the vicinal methyl group and not towards the orthogonal *ortho*-tolyl group, giving an indication of the relative steric requirements of these groups. The force-field calculations give qualitatively correct results but the quantitative agreement is rather poor.

Experimental

^{1}H N.m.r. spectra were recorded on JEOL MH-100 and Nicolet 360 WB instruments, and u.v. and c.d. spectra on Beckman model 25 and JASCO J-41A spectrometers respectively. Molecular mechanics calculations were performed by the MMP2 program developed by Allinger and co-workers.[12] Bandshape calculations and geometry modelling were performed on a PDP 11/34 computer with a GT 42 graphics terminal and a Printronix lineprinter/plotter of the Computer Graphics Laboratory for Organic Chemistry of the University of Lund. Bandshape analysis was done as previously described.[13] Chromatographic resolution was performed on a column of swollen, microcrystalline triacetylcellulose (30 × 2.5 cm, particle size 20–30 μm) in 95% ethanol at room temperature and a pressure of 1.1 kg cm^{-2} (flow-rate 165 ml h^{-1}) with u.v. (254 nm) and polarimetric (364 nm) detection. Kinetic racemization was measured by recording the decrease in optical rotation of *ca.* 4 mg of enriched material in 1 ml of propanol. The temperature was measured with calibrated thermometers in the circulating water before and after passage of the cell. Rate constants were evaluated over 1–1.5 halflives by linear regression analysis according to the equation $\log (\alpha_0/\alpha_t) = k_{rac} \cdot t$. Thermodynamic parameters for the rotational barrier were obtained from the Eyring equation using $k_{rot} = 0.5\, k_{rac}$.

The styrene (1) was prepared by reductive coupling of *o*-methylacetophenone and di-isopropyl ketone according to McMurry *et al.*[14] in 61% yield (g.l.c.) and was purified by preparative g.l.c. (OV 101; 3 m; 180 °C); *m/e* 216 (16%), 201 (3), 173 (100), 159 (32), 145 (21), 131 (77), 119 (22), 105 (19), 97 (19), 91 (27), 77 (16), 65 (15), and 57 (34); δ_H ([$^2H_6$]dimethyl ether) 0.82 and 0.89 (6 H, 2 × d, *J* 7.8 Hz), 1.30 (6 H, d, *J* 7.8 Hz), 1.90 (3 H, s), 2.20 (3 H, d, *J* 0.43 Hz), 2.28 (1 H, septet, *J* 7.8 Hz), 2.60 (1 H, septet, *J* 7.8 Hz), and 6.87–7.15 (4 H, m).

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PAPER IV

Correspondence and proofs should be sent to: Dr. Ulf Berg,
Organic Chemistry 3, Chemical Center, University of Lund,
P.O. Box 124, S-221 00 Lund, Sweden

Conformational Equilibria and Torsional Barriers of the Isopropyl Groups in N,N-Di-isopropylbenzamide and its Thio and Seleno Analogues

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Ulf Berg* and Ingrid Pettersson

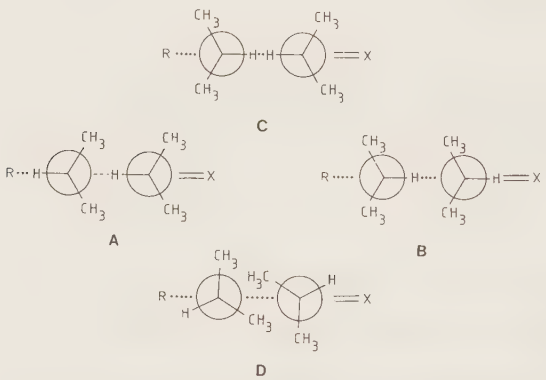
Organic Chemistry 3, Chemical Center, University of Lund,
P.O. Box 124, S-221 00 Lund, Sweden

The conformations of the isopropyl groups and the barriers to conformational interconversion in N,N-di-isopropylbenzamide (1), and its thio (2) and seleno (3) analogues have been studied with dynamic ^1H NMR spectroscopy. In 1 only one conformation is observed, whereas 2 and 3 exist as mixtures of three conformations. The use of the strongly deshielding C = X (X = O, S, Se) group and comparison with earlier results on similar systems enables total assignment, in the case of 2 rectifying an earlier proposal. The temperature dependence of the NMR spectra of 2 and 3 clearly shows that the E- and Z-isopropyl groups rotate with very different rates, thus providing an experimental evidence for the stepwise nature of the conformational interchange.

* Author to whom correspondence should be addressed.

INTRODUCTION

The conformations and barriers to conformational interchange of the isopropyl groups in N,N-di-isopropylamides, thioamides and selenoamides have been extensively studied.[1-8] Four general types of conformations, A-D, Scheme 1, exist, and their relative energies depend on the effective sizes of the flanking groups, R and X.



Scheme 1.

Usually conformations of types A and B predominate, and form B is favoured by a large X combined with a small R, whereas a small X and a large R favour form A. Conformations of type D should be regarded as an equilibrium between two rapidly exchanging enantiomers and is favoured by two large flanking substituents, R and X. Many N,N-di-isopropylthioamides and selenoamides have been shown to exist as a mixture of A, B, and in some cases D.[1-3] The conformations of the isopropyl groups in N,N-di-isopropylthiobenzamide have been studied with ^{1}H NMR at low temperature by Ramey *et al.*[7] The authors report two conformations, the major of which is suggested to be of type D and the minor of type B. This is at variance with the general

behaviour of other N,N-di-isopropyl(thio)amides.[1-3] We decided to make a reinvestigation of the conformations of the isopropyl groups in N,N-di-isopropylthiobenzamide (2) and to include the oxygen (1) and seleno analogues (3) in this study.

EXPERIMENTAL

Syntheses

N,N-Di-isopropylbenzamide (1) was prepared from di-isopropylamine and benzoyl chloride in toluene in quantitative yield, giving white prisms, m.p. 72-74 °C (litt. 69-71 °C)[9]. ^{1}H NMR ([$^2H_6$]dimethyl ether, 25 °C) δ 1.30 (12H, broad), 3.67 (2H, broad), 7.23-7.35 (5H, m).

N,N-Di-isopropylthiobenzamide (2) was prepared according to Ref. 10 from 1 in quantitative yield, giving yellow prisms, m.p. 100-102 °C (litt. 99-100 °C)[7]. ^{1}H NMR ([$^2H_6$]dimethyl ether, 25 °C) δ 1.15 (6H, d, J = 7.00 Hz), 1.75 (6H, broad), 4.10 (2H, sept., J = 7.00 Hz), 7.05-7.28 (5H, m); m/e 221 (12 %), 178 (25), 162 (5), 121 (100), 105 (52), 77 (31), 51 (10), 41 (24).

N,N-Di-isopropyl-α-methylthiobenzylidenimmonium iodide was prepared from 2 and methyl iodide in 74 % yield as colourless crystals, m.p. 141-143 °C.

N,N-Di-isopropylselenobenzamide (3) was prepared according to Ref. 11 from N,N-di-isopropyl-α-methylthiobenzylidenimmonium iodide in 26 % yield giving yellow prisms, m.p. 113-114 °C (litt. 112.0-113.5 °C)[12]. ^{1}H NMR ([$^2H_6$]dimethyl ether, 25 °C) δ 1.16 (6H, d, J = 6.80 Hz), 1.85 (6H, broad), 4.18 (2H, sept., J = 6.80 Hz), 7.04-7.28 (5H, m); m/e

269 (11 %), 226 (13), 169 (38), 146 (7), 123 (31), 104 (100), 91 (12), 77 (50), 58 (78), 51 (19), 41 (94).

^{1}H NMR spectra were recorded on a Nicolet 360 WB spectrometer. The samples were about 0.04 M in [$^2H_6$]dimethyl ether,[1] and they were degassed by the high-vacuum freeze-thaw technique before being sealed off. Me_4Si was used as internal reference. Bandshape analysis was performed as previously described.[13] The free energy differences and the free energies of activation were calculated using eqs. (1) and (2) where p_A is the fractional molar population of conformation A.

$$\Delta G^o = 1.987 \cdot 10^{-3}\ T \ln \frac{p_A}{p_B} \text{ kcal mol}^{-1} \qquad (1)$$

$$\Delta G^{\ddagger} = 4.575 \cdot 10^{-3}\ T\ [10.319 + \log \frac{T}{k}] \text{ kcal mol}^{-1} \qquad (2)$$

The bandshape calculations were performed on a PDP 11/34 computer with a GT 42 graphics terminal and a Printronix lineprinter/plotter of the Computer Graphics Laboratory for Organic Chemistry at the University of Lund.

RESULTS

The ^{1}H NMR spectra at ambient temperature indicate that the rotation around the N-C(=X) bond is slow for 2 and 3, but still has some influence on the bandshape for 1. The barriers to rotation around this bond in N,N-dimethylbenzamide and its thio, seleno and telluro analogues have been studied elsewhere[14] and will not be treated here.

Chemical shifts of the isopropyl groups and fractional populations at low temperature are shown in Table 1, and the free energy barriers to isopropyl group rotation in Table 2.

N,N-Di-isopropylbenzamide (1)

At ambient temperature, the NMR signals for 1 are broad due to fast amide bond rotation. On lowering the temperature the signals sharpen (-45 ^{o}C) and remain sharp at still lower temperature (-90 ^{o}C), and only two doublets and two septets were observed for the isopropyl ^{1}H NMR resonances.

N,N-Di-isopropylthiobenzamide (2)

The NMR spectrum for 2 shows two signals for the E- and Z-isopropyl methyl groups, at ambient temperature, due to slow amide bond rotation. The NMR signal for the Z-isopropyl methyl groups is broad and, on lowering the temperature, the signal splits into two doublets of the relative intensities 0.95:0.05 (-46 ^{o}C). The Z-methine resonance behaved similarly, giving rise to a major septet at δ4.0 and a minor septet at δ 6.1 below -46 ^{o}C. At still lower temperature a broadening of the minor component sets in and the signals split, at -102 ^{o}C, into two sets of signals with the relative intensities 0.35:0.65. The barrier for the process which leads to decoalescence at -46 ^{o}C is 13.2 ± 0.2 kcal mol^{-1} (269 K) and for the second process 9.3 ± 0.2 kcal mol^{-1} (198 K).

N,N-Di-isopropylselenobenzamide (3)

In conformity with 2 the NMR spectrum for 3 shows two doublets for the E- and Z-isopropyl methyl groups, at ambient temperature, and the

signal for the Z-isopropyl methyl groups is broad and undergoes decoalescence at -33 °C to two sets of signals with the relative intensities 0.81:0.19. At still lower temperature the signals for the minor component broaden (-70 °C) and split into two sets of signals (-105 °C) with the relative intensities 0.26:0.74, Figure 1. The barrier for the process which leads to decoalescence at -33 °C is 13.7 ± 0.2 kcal mol^{-1} (291 K) and for the second process 8.9 ± 0.2 kcal mol^{-1} (216 K).

DISCUSSION

The chemical shift for a Z-isopropyl methyl group in N,N-di-isopropyl-amides is found at ca. δ 1.40 when it points towards the carbonyl group and at ca. δ 1.10 when it is turned away from the carbonyl group.[1-3] The chemical shift for a Z-methine hydrogen is found at δ 4.5-5.2 when it points towards the carbonyl group and at δ 3.3-3.6 otherwise.[1-3] In view of these results we ascribe the only observed rotamer for 1 to a conformation of type A. This is in agreement with other amides where the carbonyl group also has been shown to have small steric requirements.[1-3]

The chemical shift for a Z-isopropyl methyl group in N,N-di--isopropylthioamides is found at δ 1.7-1.8 and for a Z-methine hydrogen at δ 5.5-6.3 when it points towards the thiocarbonyl group.[1-3] The corresponding values are δ 1.2-1.4 and δ 3.8-4.1 when the isopropyl group is turned away from the thiocarbonyl group.[1-3] In view of results obtained on several similar systems we consider the previous assigment by Ramey et al. for 2[7] as incorrect. A more likely assignment for the major rotamer is a conformation of type A,

and the two minor components we ascribe to conformations of type B and D.

In order to assign these rotamers we make use of the positions of the Z-isopropyl methyl signals (δ 1.48 and δ 1.28) and the methine septets (δ 5.95 and δ 6.03). The attribution of B and D rests on the assumption that the predominant difference in chemical shift between B and D should come from the van der Waals' shift induced in the Z-isopropyl methyl group resonance in conformation D and the position of the E-isopropyl methyl doublet at high field (δ 1.04 and δ 1.06) in conformation B, as expected for protons situated in the shielding region of the benzene ring. The same arguments are valid for the seleno compound. A typical shift for a Z-isopropyl methyl group in N,N-di-isopropylsubstituted selenoamides is ca. δ 1.85 when pointing towards the selenocarbonyl group and δ 1.3-1.5 when turned away from it.[2] A Z-isopropyl methine hydrogen is found between δ 6.3 and 6.5 when it is turned towards the selenocarbonyl group and at ca. δ 4.15 when it is turned away from the selenocarbonyl group.[2]

In all the compounds 1-3 conformation A is strongly preferred, and one can conclude that the bulky face of the isopropyl group, the methyl groups, accommodate much better with the C=X groups then with the phenyl group. This could be compared with the structurally related α-alkyl-β,β-di-isopropylstyrenes[15] in which the isopropyl groups interact with the phenyl group and the α-alkyl substituent. If the α-substitutent is a methyl, ethyl or isopropyl group there is more than 98 % of the conformation where the isopropyl groups turn the methyl groups towards the α-substituent. A much bulkier group, such as the t-butyl group, is required in order to reverse the conformational preference.

The difference in populations between A and B + D diminishes in the series X = O, S and Se, i.e. with increasing size of X. The size of X is important in two respects, on one hand in the interaction with the Z-isopropyl group and on the other in the interaction with the phenyl group which affects the dihedral angle between the N-C(X) part and the phenyl ring. Both of these effects tend to displace the equilibrium towards conformation B when the size of X is increased. The dihedral angle between the amide plane and the phenyl ring in N,N-dimethylthiobenzamide is 63° in the crystal.[16] This angle could be expected to be somewhat larger in N,N-di-isopropyl derivatives than in the corresponding N,N-dimethyl compounds and of the same magnitude as the angle between the phenyl ring and the double bond in α-alkyl-β,β-di-isopropylstyrenes.[15] The twist angle in these compounds (α-alkyl = Me, Et, i-Pr, neo-Pent, and t-Bu) is ca. 70-90° according to molecular mechanics calculations. A large twist between the amide plane and the phenyl ring is also revealed from the chemical shift of the E-isopropyl methyl groups in conformation B of 2 and 3 (δ 1.04 and 1.06, respectively).

The difference in population between conformations of type B and D for 2 and 3, 0.65:0.35 and 0.74:0.26, respectively, could also be understood when regarding the dihedral angle around the pivot bond, which is supposed to be larger in the selenoamide, 3, as discussed above.[14] This reduces the steric interaction between the E-isopropyl methyl groups and the phenyl ring in 3 compared to 2 and favours conformation B in the seleno compound relative the thio compound.

The effective size of the groups in these and analogous systems[1,2,3,15] can be estimated from the position of the conformational equilibria:

H ≈ C=O < i-Pr < Me ≈ Et ≈ n-Pr < C=S < C=Se < Ph < CF_3 ≈ t-Bu.

The assignments made above lead to the conclusion that the decoalescence observed at -46 °C for 2 and at -33 °C for 3 corresponds to the rotation of the Z-isopropyl group. The barrier for this rotation is slightly higher in 3 than in 2 (Table 2), possibly depending upon the larger size of Se than S. The process affecting the spectrum at lower temperature consequently is the rotation of the E-isopropyl group, and, in contrast to the aforementioned process, the barrier is slightly lower for 3 than for 2. Of more significance, however, is the difference in torsional barrier between the E- and Z-isopropyl groups in both 2 and 3. The rate constant for the rotation of the E-isopropyl group is roughly five powers of magnitude larger than the rate constant for rotations of the Z-isopropyl group ($\Delta S^{\ddagger}$ assumed zero in both cases) thus providing a very clear evidence for a stepwise nature of the conformational interchange, A ⇄ B. A comparison with earlier work[1,2] shows that the barrier to isopropyl rotation in N,N-di-isopropylthio- and seleno-amides fall in the range 12-14 kcal mol^{-1} and, thus, the E-isopropyl barriers of 2 and 3 are low, whereas the Z-isopropyl barriers stay in the normal region. The low E-isopropyl barrier depends largely on a comparatively low transition-state energy, probably invoked by a higher degree of planarity of the Ph-C(X) system with concomitant more effective conjugation, and only to a minor part on high ground-state energies of the rotamers B and D.

CONCLUSIONS

The conformations of the isopropyl groups in N,N-di-isopropylbenzamide (1) and the corresponding thio- (2) and seleno- (3) analogues

have been studied with dynamic ^{1}H NMR spectroscopy. Compound 1 was shown to exist in only one conformation at low temperature. This conformation was ascribed type A (Scheme 1). 2 and 3 were shown to exist in three conformations, A, B, and D, with the relative intensities 0.95:0.035:0.015 and 0.87:0.104:0.026, respectively. The barrier for the Z-isopropyl group rotation for 2 was 13.2 ± 0.2 kcal mol^{-1} and for 3 13.7 ± 0.2 kcal mol^{-1}. The barrier to E-isopropyl group rotation was 9.3 ± 0.2 and 8.9 ± 0.2 kcal mol^{-1} for compounds 2 and 3, respectively. The mechanism for the exchange A $\rightleftharpoons$ B was shown to be a stepwise rotation of the isopropyl groups.

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Table 1. Chemical shifts[a] and fractional populations of compounds 1-3

Compd	Temp, °C	Rotamer A					Rotamer B					Rotamer D				
		CH_3-Z	CH-Z	CH_3-E	CH-E	p[b]	CH_3-Z	CH-Z	CH_3-E	CH-E	p[b]	CH_3-Z	CH-Z	CH_3-E	CH-E	p[b]
1	-90	1.52	3.81	1.12	3.53	1.0										
2	-110	1.81	4.03	1.13	4.03	0.95	1.28	6.03	1.04	4.03	0.035	1.48	5.95	1.13	4.03	0.015
3	-105	1.92	4.20	1.15	4.10	0.87	1.33	6.25	1.06	4.20	0.104	1.55	6.10	1.15	4.40	0.026

[a] In ppm downfield from internal Me_4Si, in dimethyl-d_6 ether.

[b] Fractional population.

Table 2. Free energy barriers to isopropyl group rotation in compounds 2-3

Compd	Temp, K	$\Delta G^{\ddagger}_{-}$ A→(B+D) kcal/mol	Temp, K	$\Delta G^{\ddagger}_{-}$ D→B kcal/mol
2	269	13.2 ± 0.2	198	9.3 ± 0.2
3	291	13.7 ± 0.2	216	8.9 ± 0.2

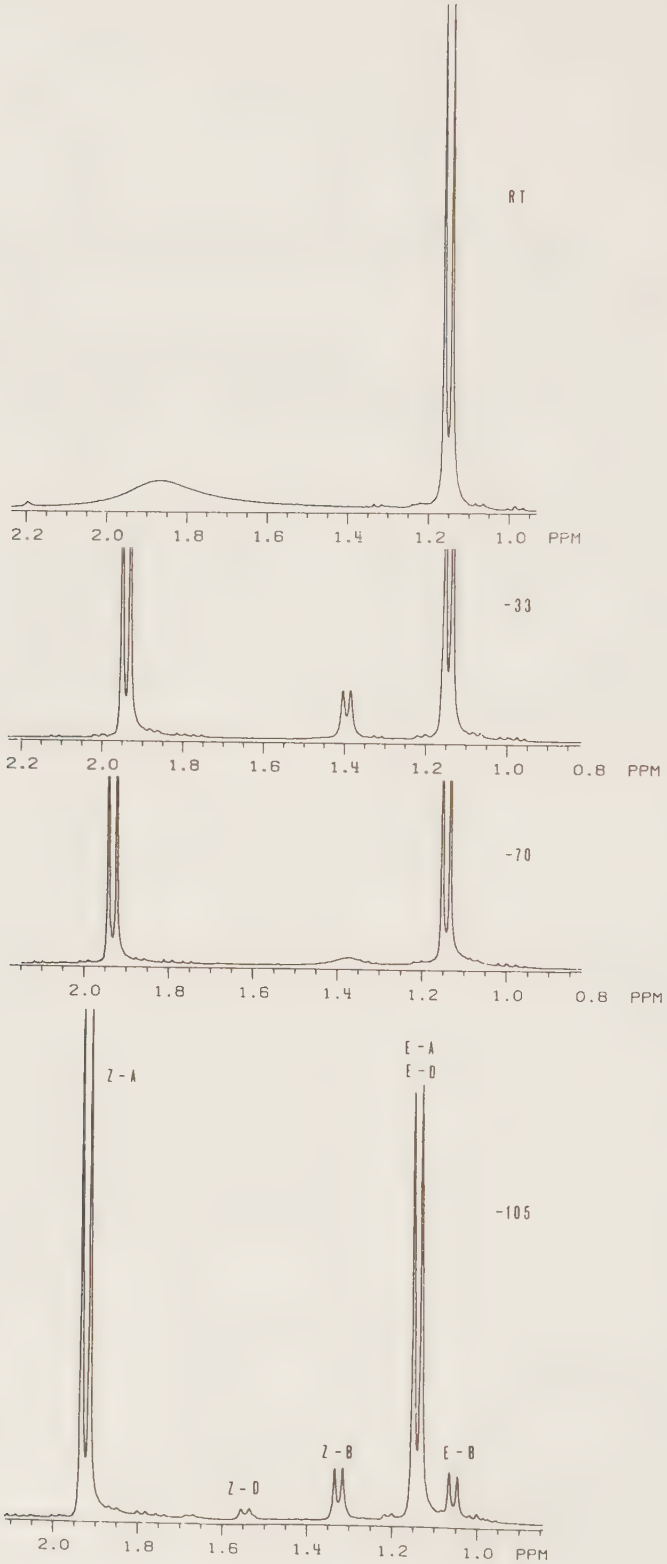

Figure 1. 360 MHz ^{1}H NMR spectrum of 3 in [$^{2}H_{6}$]dimethyl ether at different temperatures showing the isopropyl doublet region.

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Correspondence and proofs should be sent to
Dr. Ulf Berg, Organic Chemistry 3, Chemical Center, University of Lund,
P.O. Box 740, S-220 07 Lund, Sweden

Static and Dynamic Stereochemistry of Tetra-primary-alkylethylenes

Leif Andersen,[a] Ulf Berg,[b*] and Ingrid Pettersson[b]

[a] Department of Inorganic Chemistry, Chalmers University of Technology, S-412 96 Göteborg, Sweden, and [b] Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 740, S-220 07 Lund, Sweden

The stereochemistry of tetra-ethyl (1), -propyl (2), -isobutyl (3), -neopentyl (4), and -benzyl (5) -ethylene has been investigated by dynamic ^{1}H NMR spectroscopy, X-ray analysis (for 5) and molecular mechanics calculations (MM2, MMP2 force fields). The benzyl groups of 5 project alternately above and below the least-squares ethylene plane in the crystal. The NMR spectra of 3 and 4 are in agreement with a similar up-and-down conformation and molecular mechanics calculations predict ground-state structures of the same type (D_2 symmetry) for 1-4, but not for 5. Arguments are presented that the molecular mechanics force field fails to reproduce the interaction potential for two benzene rings, leading to unreliable calculated conformational stabilities of 5. The barrier ($\Delta G^{\ddagger}_{T_c}$) to site exchange of the alkyl groups is in 1, 2, and 5 $\leq$ 6.5 kcal/mol, in 3 8.6 kcal/mol and in 4 19.8 kcal/mol ($\kappa = \frac{1}{2}$), in the latter case rectifying an earlier

reported value. A gas-phase NMR study of 4 indicates that the barrier is at least 1.5 kcal/mol higher than in solution. According to the calculations the alkyl group rotations are not concerted and the calculated barrier of 3 is in excellent agreement with the experimental value. Relative rates of epoxidation by m-chloroperbenzoic acid, obtained by a competition method, are: 1-octene: 0.4 ± 0.5, 1: 17 ± 5, 2: 16 ± 2, 3: 1.0, and 5: 0.003 ± 0.001 whereas 4 was inert under the reaction conditions.

Sterically congested molecules have attracted considerable interest both as synthetic targets and as subjects for investigations of structure and physico-chemical properties.[1] One such class of compounds is tetraalkylethylenes, with tetraisopropylethylene[2] and the hitherto elusive tetra-tert-butylethylene as notable representatives. These molecules have attracted interest for somewhat different reasons. Tetra-tert-butylethylene is predicted to be highly strained, with a calculated (molecular mechanics, MMI) strain energy of 100 kcal/mol, and to be twisted by ca. 45° around the double bond.[3,4] Tetraisopropylethylene, on the other hand, is not exceptionally strained (strain energy 18 kcal/mol), is planar and has a "gear-meshed" conformation (C_{2h} symmetry).[4-6]

This report deals with the stereochemical features of some tetra-primary-alkylethylenes, of which two, tetrabenzyl-[7] and tetraneopentylethylene[8] have been investigated previously. The study covers dynamic ^1H NMR spectroscopy, X-ray crystallography, molecular mechanics calculations, and some reactivity experiments of $R_2C = CR_2$ with R = ethyl (1), propyl (2), isobutyl (3), neopentyl (4), and benzyl (5).

Tetraneopentylethylene, 4, was studied by Olah and Prakash,[8] and, based upon its NMR spectrum, a conformation with the neopentyl groups pointing alternately up and down around the perimeter of the double bond was deduced. A barrier to rotation of the neopentyl groups of 21.7 kcal/mol at 145 °C was evaluated by bandshape analysis.

Richardson and Gunderson observed a singlet for the methylenic protons in the ^{1}H NMR spectrum of tetrabenzylethylene, 5,[7] in the temperature range 30 to -30 °C and concluded that "the 'cogwheel' effect is inoperative" with 5. From model inspections the authors suggested minimum-energy conformations with two trans-benzyl groups lying in the plane of the sp^2 framework and the other two above and below the plane.

In view of our experience with the conformation of alkyl groups, including benzyl groups, attached to planar frameworks, we found reasons to question these conclusions.[9] First, primary alkyl groups, essentially without known exceptions, prefer up-and-down conformations of the type suggested for 4, and, second, the barrier to rotation of benzyl groups in such systems is much too low to be observed by NMR at temperatures as high as -30 °C.

Results and Dicussion

Dynamic ^{1}H NMR Spectroscopy. The 360 MHz ^{1}H NMR spectra of 1, 2, 3, and 5 in dimethyl-d_6 ether showed no sign of geminal diastereotopism and contained only sharp signals at ambient temperature. Furthermore, the spectra of 1, 2, and 5 did not change down to ca. -140 ^{o}C, and, thus, little information as to conformation or rotational barrier could be obtained by dynamic NMR for these compounds.

The spectrum of 3, however, experienced band-broadening below -70 ^{o}C and at -115 ^{o}C both the methylene protons and the methyl groups showed geminal diastereotopism. Only one set of signals was obtained indicating a single conformation within the detection limit of the experiment ($\geq$ 97 %). Bandshape analysis of exchange-broadened methyl signals in the range -80 to -100 ^{o}C gave $\Delta G^{\ddagger}_{181} = 8.8 \pm 0.2$ kcal/mol for the exchange process. We considered attempts to split the free energy into enthalpy and entropy parts too unreliable, since the temperature range in which accurate rate constants could be determined was limited to ca. 20 deg and since the temperature region for extrapolation of the chemical shift difference was inaccessible.

The temperature dependence of the ^{1}H NMR spectrum of 4 was described by Olah and Prakash.[8] At room temperature the methylene protons gave rise to an AB quartet, which coalesced to a singlet at ca. 150 ^{o}C, and the authors reported the thermodynamic parameters: $\Delta G^{\ddagger}_{418} = 21.7 \pm 0.5$ kcal/mol; $\Delta H^{\ddagger} = 11.68 \pm 0.5$ kcal/mol and $\Delta S^{\ddagger} = -20 \pm 2.0$ cal/(mol K) for the exchange process. In our hands, the spectral features of 4 in the same solvent, hexachloroacetone, were in complete agreement with those reported,[8] but we evaluated quite different rate constants and thermodynamic parameters, $\Delta G^{\ddagger}_{418} = 20.4 \pm 0.1$ kcal/mol, $\Delta H^{\ddagger} = 20.17 \pm 0.5$

kcal/mol and $\Delta S^{\ddagger} = -0.6 \pm 1.2$ cal/(mol K).[10] The errors given for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are one standard deviation from a least squares Eyring plot. Both sets of data were calculated using a transmission coefficient of 1, a value not entirely justified considering the rearrangement mechanism at operation (see below).

The advent of pulse NMR technique and high-field, superconducting magnets has offered the opportunity of gas-phase NMR studies. Although 4 is a rather large molecule, 66 atoms, its low polarity and spherical shape should lead to sufficiently high vapour pressure at temperatures higher than ca. 100 °C, to enable the determination of conformations and rates of isomerization in the gas phase. At 120 °C, the NMR spectrum of gaseous 4 showed the expected singlet for the tert-butyl groups, and an AB spectrum ($\Delta\delta$ = 0.76 ppm) for the methylene protons, although the fine structure was not resolved due to natural line broadening. The tert-butyl signal served as resolution standard, and using the T_2 values derived from the line width of this signal (ca. 25 Hz), the bandshape of the AB quartet could be perfectly reproduced. At 155 °C, which was the high temperature limit, essentially no sign of broadening due to exchange was observed, and a higher limit of the rate constant of 60 s^{-1} could be derived corresponding to a lower limit of 21.9 kcal/mol for the barrier.

Finally, we also searched for restricted rotation of the tert-butyl groups in 4, but all NMR signals remained sharp down to -130 °C in dimethyl-d_6 ether at 360 MHz.

Static Stereochemistry. The dynamic NMR results accounted for above give only limited information as to the stable conformation of these molecules. Thus, essentially nothing was learned for 1, 2, and 5, but even for 3 and 4 several possible conformations are compatible with the spectroscopic features.

The conformations of primary alkyl groups attached to sp^2-hybridized frameworks have been investigated in several systems,[9] and it seems that, essentially without exception, such groups prefer a conformation roughly perpendicular to the planar framework. In the case of tetra-primary-alkylethylenes this leads to five idealized rotational isomers as shown in Table I. The formalism parallels the one recently presented for tetra-o-tolylethylene.[12] Two of the isomers, $I_3/\bar{I}_3$ and $I_{2t}/\bar{I}_{2t}$ are chiral. However, the protons of any methylene groups in all rotational isomers (and in certain residual diastereomers) are geminally diastereotopic, and, as is seen in Table I, only the $I_3/\bar{I}_3$ pair can be excluded as conformational candidates for 3 and 4 on the basis of the multiplicity of the NMR spectrum alone. In order to gain further knowledge the relative energies of the isomers must be known and for that purpose we resorted to molecular mechanics calculations.

Molecular mechanics calculations, using the MM2 (or MMP2) force field,[13] support the premise of the five rotational isomers in Table I as the stable conformations of 1-5. The enthalpy differences between the isomers are presented in Table II and steric energy, heat of formation and strain energy values are given in Table III. The results presented in Table II predict $I_{2t}/\bar{I}_{2t}$ to be the most stable isomer for 1-4 (5 will be treated below), and in the cases of 3 and 4 the only

detectable isomer, in agreement with the proposal of Olah and Prakash. Interestingly, conformer I_4, with all alkyl groups projecting toward the same side, is rather stable for 1 and 2 but has rapidly increasing energy in 3 and 4, whereas conformer I_{2c} shows the opposite trend. It is also notable that I_{2g} has higher energy than I_3 throughout the series.

Selected structural parameters for the predicted ground-state conformers, $I_{2t}/\bar{I}_{2t}$, are given in Table IV. The twist around the double bond in 4 removes the trans-syn alkyl groups from each other, whereas it brings them closer in 3. Likewise, the changes in the dihedral angles, φ, are not readily rationalized.

The major factor that governs the conformational energies in this series is the van der Waals interaction between the alkyl groups. Further information of this aspect is gained by studying the three possible dialkylethylenes, 1,1-, cis-1,2-, and trans-1,2-dialkylethylene. Table V reports the calculated energy difference between the syn and anti conformers of this series. The geminal and cis--vicinal configurations prefer the anti conformation, whereas the trans-vicinal configuration is somewhat more stable in the syn form. Thus, a weak van der Waals attraction, slightly increasing with the steric size of the alkyl groups (i.e. branching at the β-position), determines the conformations of the trans-vicinal arrangement, whereas repulsion dominates geminal and cis-vicinal forms. These relations were maintained when the α-methylene hydrogens were stripped off in the calculations, showing that the effects are indeed dominated by van der Waals interactions between the alkyl groups.

Now the tetraalkylethylene feature is better understood. For example, all interactions favor the $I_{2t}/\bar{I}_{2t}$ conformer, and the I_{2g} conformer contains two of the least favourable syn-geminal interactions.

The Structure of Tetrabenzylethylene, 5. Molecular mechanics calculations, MMP2, predict perpendicular conformers also for 5, but the relative energies of the different isomers deviate strikingly from those of 1-4 (Table II). Thus, isomer I_{2g} is predicted to be the, by far, most stable conformer. Furthermore, the conformation suggested by Richardson and Gunderson[7] was calculated to be a local energy minimum, although 4.0 kcal/mol higher in energy than I_{2g}.

In order to acquire experimental information, the molecular structure of 5 was determined by X-ray analysis. The crystals are monoclinic, space group C 2/c with twelve molecules per unit cell.The crystal contains molecules with two slightly different structures called 5a and 5b.

Some selected bond lengths and bond angles are reported in Table VI, and dihedral angles in Table VII.The two different molecules in the unit cell, 5a and 5b, have quite similar structures and both belong to the rotational isomer class I_{2t}. Structure 5b has a proper C_2 axis along the double bond and two orthogonal, pseudo C_2 axes, whereas 5a has three orthogonal, pseudo C_2 axes. Interestingly, there are three intermolecular contacts of very similar character between the two molecules. In these contacts a phenyl group from one molecule is essentially perpendicular to a phenyl group from the other molecule. This arrangement is quite similar to the most stable structure of the benzene dimer (see below).

The question arises, whether the disparity between calculated

and X-ray structures of 5 is due to crystal packing forces, or to some deficiency in the molecular mechanics procedure. Although, one can not, a priori, exclude other conformations in solution or in the gas phase than in the crystal, we favour the latter alternative since it is our feeling that molecular mechanics calculations of systems containing two closely spaced, face-to-face benzene molecules tend to exaggerate the attractive interactions between the benzene moieties. Among the rather few cases in which experimental and calculated values are available we single out heat of formation of cyclophanes. As shown in Table VIII the calculations strongly underestimate the heats of formation of those systems in which the aromatic rings have the "en-face" geometrical relation, i.e. in 2,2-metapara-, 2,2-para-, and 3,3-paracyclophane by ca. 10 kcal/mol, but reproduce the value for 2,2-metacyclophane, in which the two rings have another geometrical relation.

Another piece of evidence was found in calculations by the MMP2 force field on the interactions between two benzene molecules in the parallel and the perpendicular configurations. Figure 1 shows a comparison of the potential energy curves from these calculations with two other approaches, ab initio SCF CI calculations[14] and empirical potentials obtained from the second virial coefficients.[15] It is seen that the perpendicular arrangement, known to be the most stable one,[16] is about 1 kcal/mol less binding in the molecular mechanics calculations than in the other potentials. On the other hand, the molecular mechanics force field predicts the parallel energy-minimum geometry to be as much as 1.5 kcal/mol more stable than the empirical potential, let alone the ab initio potential. Furthermore, the authors of both papers argue that the empirical potential is probably too

binding for the parallel geometry.[14,15] The minimum-energy distances are, however, in good agreement for all three potentials, and the geometry of the perpendicular arrangement accords with the three intermolecular phenyl-phenyl contacts in the crystal of 5, mentioned above. A closer examination of these potential curves and their origin in terms of e.g. electrostatic and quadrupolar effects or nonspherical van der Waals potentials, is beyond the scope of this paper, let us only mention that inclusion of electrostatic interactions, using localized atomic charges of 0.11 a.u., gives a potential curve essentially concurring with the empirical one. The two pairs of geminal phenyl groups of the I_{2g} isomer of 5 are calculated to have a geometry very close to the minimum energy geometry of two parallel benzene molecules. Not surprisingly, then, inclusion of the same atomic charges as above, in the calculations on 5 predicts I_{2t} to be more stable than I_{2g} by 1.96 kcal/mol. For the reasons given, we believe that 5 belongs to the rotational isomer class $I_{2t}/\bar{I}_{2t}$ also in the gas phase and in solution.

Dynamic Stereochemistry. The rate processes observed by DNMR for 3 and 4 correspond to rearrangement from the ground-state conformer, I_{2t}, to its enantiomer, $\bar{I}_{2t}$. This is a rather complex transformation which involves rotation of four alkyl groups through the olefin plane and may, hypothetically, proceed through different mechanisms. A complete description of the modes of isomerization in an analogous system has recently been published.[12] The relevant pathways are presented in Figure 2. In one extreme, four groups rotate in a concerted fashion in a one-step process, and in the other extreme, a stepwise rotation of one group at a time over three intermediates is operating. In order to decide among these alternatives,

molecular mechanics calculations were performed on 1 and 3, using the incremental group driving technique and the MM2 program. We avoided the pitfalls inherent in the driving technique by starting both at the nearest stationary states and at peaks of high energy near the local transition states. Furthermore, calculations were not performed on the neopentyl derivative, 4, which is more susceptible to such errors than 1 and 3.

According to the calculations the rearrangement proceeds through a completely uncorrelated, four-step mechanism. Simultaneous rotation of two or more groups leads to barriers which are at least twice as high as for the single group rotation. The calculated barrier heights are 3.7 kcal/mol for 1 and 8.8 kcal/mol for 3 ($I_{2t} \rightarrow I_3$ in both cases), the latter value being in excellent agreement with experiment. In both 1 and 3 rotation of one alkyl group past the geminal neighbor has significantly lower energy than rotation past the vicinal neighbor by ca. 2 and 3 kcal/mol, respectively. A closer look at the predicted mode of isomerization M_1, reveals three alternative pathways over the achiral rotamers I_{2g}, I_{2c} or I_4. For isomerization of 1 the local transition states leading to the intermediates I_{2c}, I_4 and I_{2g} are 1.9, 2.8, and 1.9 kcal/mol, respectively, above the energy of I_3, and the corresponding values for 3 are 2.2, 3.1, and 4.2 kcal/mol. The energy profile for rearrangement of 3 is shown in Figure 3. These profiles involve passage over four nearly equienergetic transition states and the use of transmission coefficient $\kappa = 1/2$ or 1/4 appears more realistic than a value of unity used above. This applies also for 4, since in all likelihood, it has an energy profile similar to 1 and 3, and, for symmetry reasons, certainly has two equienergetic

transition states. A value of $\kappa = 1/2$ gives for 3; $\Delta G^{\ddagger}_{181} = 8.6$ kcal/mol and for 4; $\Delta G^{\ddagger}_{418} = 19.8$ kcal/mol and $\Delta S^{\ddagger} = +0.83$ cal/(mol K), whereas $\Delta H^{\ddagger}$ does not change. In any case, $\Delta S^{\ddagger}$ is close to zero, within experimental accuracy. Considering statistical contributions to the entropy of activation the effect of symmetry number to $\Delta S^{\ddagger}$ is $+ R \ln 4$.[17a] On the other hand, slightly negative entropy contributions are often found in processes in which alkyl groups are squeezed past each other in the transition state due to decreased rotational freedom of the encumbered alkyl groups.[17b] Thus, taken as a whole, a $\Delta S^{\ddagger}$ value close to zero seems very likely.

The barrier to rearrangement of 4 is significantly higher, by at least 1.5 kcal/mol, in the gas phase than in solution. Not too many gas-phase values for conformational processes determined by DNMR exist and most studies hitherto reported deal with polar molecules, such as amides[18] and nitrosamines.[19] In those systems the rotational barriers are generally 1-2 kcal/mol lower in the gas phase. One example with a nonpolar system, the ring inversion of cyclohexane,[20] shows that even in the absence of strong electrostatic interactions the barrier can be phase dependent. Higher gas-phase activation parameters are usually explained by a process proceeding *via* a transition state that is smaller than the ground state and *vice versa*. In the case of 4, however, we cannot rule out other explanations considering the rather complex rearrangement mechanism *via* stepwise rotation of the four alkyl groups. If this process requires more than one activation and thus more than one collision,

the lower pressure in the gas phase would lead to substantially increased barrier.

Reactivity and Steric Hindrance. The inert character of 4 and 5 to electrophilic attack at the double bond was demonstrated in earlier papers,[7,8] and was interpreted in terms of steric hindrance. Thus, 4 is completely inert to bromine and showed no evidence of protonation in superacidic medium, $HOSO_2F/SO_2ClF$,[8] whereas 5 adds bromine only slowly.[7] Attempts at determining the relative rates of bromination of 1-5, however, met with difficulties. Thus, some solutions turned dark violet shortly after addition of bromine, even when kept in the dark, and GC analysis revealed the existence of decomposition products.

Instead, we found that epoxidation of the olefins with m-chloroperbenzoic acid gave stable epoxides in clean reactions according to GC/MS and NMR analysis.Such epoxidation has earlier proven useful in establishing steric effects of alkylethylenes.[21,22] The relative rates of epoxidation with m-chloroperbenzoic acid in methylene chloride at 20 ^{o}C, determined with a competition technique, were: 1-octene: 0.4 ± 0.5, 1: 17 ± 5, 2: 16 ± 2, 3: 1.0, and 5: 0.003 ± 0.001. 4 gave no reaction. These results may be rationalized in terms of two opposing effects: (i) the rate is greatly increased by electron-donating alkyl substituents and epoxidation is therefore clearly an electrophilic addition, (ii) steric effects strongly decrease the reactivity for the heavily substituted ethylenes 4 and 5. Similar results have been observed for bromination.[23] The hindrance to attack is easily understood in view of the stereochemistry of these molecules. In the ground state conformation both sides of the double bond are protected

from attack, and other conformations, which better expose one side of the double bond, such as I_3 or I_4, have much higher energy. One striking aspect is the low reactivity of 5 compared to 3, which could hardly be predicted on the basis of the results presented in Table II. However, it should be borne in mind that the values for 5 in this table are less reliable.

In conclusion, epoxidation and bromination[7,8,24] rates of tetra-primary-alkylethylenes demonstrate the importance of both electronic and steric effects of alkyl groups in these reactions. On the other hand, it is important to recognize that these molecules are not particularly strained, as judged from the strain energies in Table III.

Conclusions

On the basis of the crystal structure of tetrabenzylethylene (5), the dynamic NMR properties of tetraisobutylethylene (3) and tetraneopentylethylene (4) in solution and, in the case of 4 also in the gas phase, as well as molecular mechanics calculations, a unified description of the conformation of tetra-primary-alkylethylenes emerges, involving an alternating up-and-down orientation of the alkyl groups. This type of conformation, here called I_{2t}, has molecular D_2 symmetry and is governed by steric attraction between *syn*, *trans* arrangements and avoidance of repulsion for *syn*, geminal and *syn*, *cis* arrangements of the alkyl groups.

Barriers to enantiomerization ($\Delta G^{\ddagger}_{T_c}$) are for 3: 8.6 kcal/mol and for 4: 19.8 kcal/mol using the value 1/2 for the transmission coefficient. The process proceeds, according to molecular mechanics

calculations, via a stepwise mechanism, in which the alkyl groups rotate one at a time.

The molecular mechanics description of the steric interaction between two benzene rings reveals that such calculations exaggerate the attraction between two face-to-face oriented benzene rings at their minimum energy distance. As a consequence the force-field calculations fail to reproduce the correct conformation of 5.

The relative rates of epoxidation by m-chloroperbenzoic acid demonstrate the importance of both electronic and steric effects in addition reactions to these olefins just as earlier shown for bromination.

Experimental Section

Materials. Tetrahydrofuran was distilled from sodium wire. All reactions were carried out under nitrogen or argon atmosphere.

3,4-Diethyl-3-hexene (1) and tetrabenzylethylene (5) were prepared according to Lenoir,[25] and 4,5-di-(2-methylpropyl)-2,7-tetramethyl-4-octene (4) was prepared according to Olah and Prakash,[8] and had characteristics in agreement with those given.

4,5-Dipropyl-4-octene (2) was prepared by the method of Lenoir[25] in 26 % yield, bp 104-106 °C (13 mm Hg); ^{1}H NMR (dimethyl-d_6 ether) δ 0.90 (t, 4 x 3 H, J 7.35 Hz), 1.39 (m, 4 x 2 H), 2.01 (distorted t, 4 x 2 H, J 7.7 Hz); mass spectrum, m/e (relative intensity) 196 (5), 111 (14), 97 (25), 83 (34), 69 (80), 55 (100). Anal. Calcd. for $C_{14}H_{28}$: C, 85.6; H, 14.4. Found: C, 85.5; H, 14.3.

4,3-Di-(2-methylpropyl)-2,7-dimethyl-4-octene (3) was prepared by the method described by Olah and Prakash[8] in 70 % yield, bp 70-73 °C (0.4 mm Hg).

The product was further purified with preparative GC on a OV 101 column (40-60 mesh, 3 m) at 170 °C. ^{1}H NMR (dimethyl-d_6 ether) δ 0.90 (d, 4x6 H, J 6.54 Hz), 1.77 (m, 4x1 H), 2.02 (d, 2 H, J 7.20 Hz); mass spectrum, m/e (relative intensity) 252 (8), 153 (5), 125 (6), 111 (12), 97 (68), 83 (69), 69 (100), 57 (98). Anal. Calcd for $C_{18}H_{36}$: C, 85.63; H, 14.4. Found: C, 84.6; H, 14.0.

^{1}H NMR spectra were recorded on a Nicolet 360 WB spectrometer. The samples were about 0.04 M in dimethyl-d_6 ether and they were degassed by the high vacuum freeze-thaw technique before being sealed.

TMS was used as internal reference. The temperature scale of the instrument was calibrated by the use of a methanol/acetone-d_6 sample, which in turn had been calibrated by the technique described in Ref. 21 using a Jeol MH-100 instrument. The high temperature ^{1}H NMR spectra for 4 were recorded on a Jeol MH-100 spectrometer. The sample was about 0.3 M in hexachloroacetone. Octamethylcyclotetrasiloxane was used as internal reference. The temperature scale was calibrated by the method described in Ref. 21. The gas-phase measurement was performed in a 5 mm Pyrex NMR tube. Hexadeuterioacetone (20 mg) was added to effect line narrowing and to ensure unimolecular kinetics. The sample was degassed by the high vacuum freeze-thaw technique before being sealed. The pressure was estimated by assuming ideal gas conditions to 2500-3000 torr (error limit ca. 20 %) in the temperature range 120-160 °C. The spectra were obtained in the unlocked mode on a spinning sample. Typically 500 transients were collected at each temperature, stored in 8 K of memory and zero-filled

to 16 K prior to Fourier transformation. Acquisition times were 1.5 s per transient.

Bandshape analysis and evaluation of thermodynamic parameters were performed as previously described.[26] Calculations were performed on a PDP 11/34 computer with a GT 42 graphics terminal and a Printronix lineprinter/plotter of the Computer Graphics Laboratory for Organic Chemistry of the University of Lund.

Kinetics. Competitive epoxidation was carried out as follows. Equal amounts (ca. 0.08 mmol) of each of two olefins were dissolved in 5 mL of methylene chloride at 20 ^{o}C and supplied with 1/20 equivalent of m-chloroperbenzoic acid. The mixture was stirred for ca. 1 h and analyzed directly on a 1.5 m x 3 mm 3 % OV 101 on Chromosorb Q column using a Varian 1400 gas chromatograph equipped with an electronic integrator (Hewlett Packard 3390 A). The relative rates were determined from the relative amounts of the corresponding epoxides produced, after correction for response factors. The epoxides have the following characteristics.

1,2-Epoxyoctane: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J 6.65 Hz), 2.46 d of d, 1 H, ^{2}J 4.6 Hz, ^{3}J 2.7 Hz), 2.74 (d of d, 1 H, ^{2}J 4.6 Hz, ^{3}J 4.6 Hz), 2.90 (m, 1 H); mass spectrum, m/e (relative intensity) 128 (3), 85 (15), 81 (20), 71 (100), 58 (73), 55 (93), 45 (19). 3,4-Diethyl-3,4-epoxyhexane: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 4 x 3 H, J 7.40 Hz), 1.37 (quartet of d, 4 x 1 H, ^{AB}J 14.4 Hz, ^{3}J 7.40 Hz); mass spectrum, m/e (relative intensity) 156 (1), 86 (39), 69 (10), 57 (100), 45 (37). 4,5-Dipropyl-4,5-epoxyoctane: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 4 x 3 H, J 7.04 Hz), 1.34-1.63 (m, 4 x 4 H); mass spectrum, m/e

(relative intensity) 213 (3), 114 (32), 99 (26), 86 (38), 71 (100), 55 (70). 4,5-Di-(2-methylpropyl)-2,7-dimethyl-4-epoxyoctane: ^{1}H NMR ($CDCl_3$) δ 0.86 (d, 4 x 3 H, J 6.40 Hz), 0.90 (d, 4 x 3 H, J 6.40 Hz), 1.45 (m, 4 x 2 H), 1.74 (m, 4 x 1 H); mass spectrum, m/e (relative intensity) 269 (2), 142 (24), 127 (48), 100 (21), 85 (90), 69 (56), 57 (100). 2,3-Dibenzyl-1,4-diphenyl-2,3-epoxybutane: ^{1}H NMR ($CDCl_3$) δ 3.08 (q, 4 x 2 H, J 14.72 Hz), 7.20-7.35 (m, 4 x 5 H); mass spectrum, m/e (relative intensity) 313 (5), 91 (100).

Molecular Mechanics Calculations were performed using the MM2 (MMP2) program developed by Allinger and coworkers employing their 1977 force field.[13]

Crystallography. Crystals suitable for X-ray analysis of 5 were obtained by slow crystallization from heptane.

Crystal data: $C_{30}H_{28}$, M_r = 388.56, monoclinic, space group C 2/c, a = 26.05 (1), b = 13.450 (7), c = 21.360 (7) Å, β = 113.18 (4)°, U = 6913 (5) Å^3, Z = 12, Dc = 1.13 Mgm^{-3}, μ(MoK_α) = 0.7 cm^{-1}. 1922 reflections with $I > 3\sigma(I)$, final R value = 0.065, R_W = 0.058. The structure was solved with MULTAN 80 which revealed the positions of all non-hydrogen atoms. The atomic positions for the hydrogen atoms were found after least-squares refinement and difference Fourier analysis. The final refinement cycle included anisotropic temperature factors for the non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms. $F_{obs} - F_{calc}$ tables can be obtained from L. Andersen at Chalmers University of Technology, Göteborg.

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Supplementary Material Available:

Figures showing the gas-phase ^1H NMR spectrum of compound 4 (Figure S1), a Pluto plot of the ground-state conformation of compound 3 (Figure S2), and a stereoview of the X-ray structure of compound 5 (Figure S3) (3 pages). Ordering information is given on any current masthead page.

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(10) The temperature dependence of the NMR spectrum of 4 and the corresponding calculated spectra were shown in Figure 1, Ref. 8. We performed bandshape analysis of these spectra and obtained a completely different set of rate constants, which gave thermodynamic parameters essentially concurring with those obtained in our original study. Although the approximate character of bandshape simulations on such small spectra is evident, the disparity was large enough for the conclusion that different mathematical expressions were used in the two cases. We checked that our bandshape program gave spectra perfectly reproducing those in Figure 6 in Ref. 11.

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Table I. Rotational Isomers of Tetra-primary-alkylethylenes, $(RCH_2)_2C{=}C(CH_2R)_2$

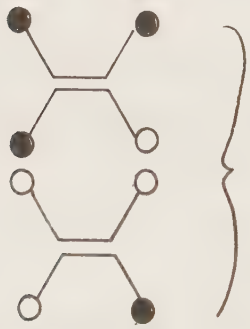
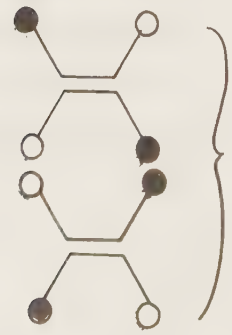
isomer	structure	symmetry point group	no. of R and CH_2 signals
I_4		C_{2v}	1
I_3		C_1	4
$\bar{I}_3$			
I_{2c}		C_{2h}	1
I_{2g}		C_{2h}	1
I_{2t}		D_2	1
$\bar{I}_{2t}$			

Table II. Relative Steric Energies (kcal/mol) of the Rotational Isomers of 1-5 Calculated by the MM2 (MMP2) Force Field

compound	I_{2t}	I_3	I_4	I_{2c}	I_{2g}
1	0	1.74	1.78	1.87	2.14
2	0	1.76	1.71	2.48	2.18
3	0	6.71	5.33	2.95	7.04
4	0	11.38	23.43	12.42	17.85
5	2.72	3.76	3.44	4.23	0

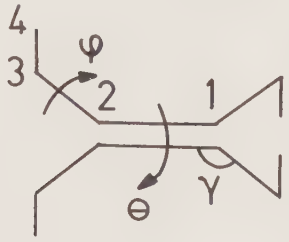
[a] MMP2 force field.

Table III. Steric Energy, Heat of Formation, ΔH_f^o, and Strain Energy for the Ground-State Conformer (I_{2t} where not otherwise stated) of 1-5 Calculated by the MM2 Force Field (kcal/mol)

compound	steric energy[a]	ΔH_f^o	strain energy
1	9.84	-36.44	7.56
2	11.77	-60.68	7.00
3	17.43	-85.89	10.72
4	28.15	-110.52	20.29
5[b]	-8.04	-10.32	-7.50

[a] Energy given by the force field without physical significance. [b] MMP2 force field on the I_{2g} conformer.

Table IV. Selected Structural Parameters for the I_{2t} Isomers of 1-4 Calculated by the MM2 Force Field



compound	r (Å)[a]	θ (deg)[b]	φ (deg)[c]	γ (deg)[d]
1	1.351	1.6	93.9 ± 0.2	123
2	1.351	1.8	93.8 ± 0.1	123
3	1.353	4.7	83.7 ± 0.0	123
4	1.358	3.8	100.9 ± 0.3	123

[a] Bond length of double bond. [b] Twist angle around double bond. [c] Mean value of the dihedral angle of the type C(1)--C(2)-C(3)-C(4) for the four alkyl groups. The "error" shows the maximum deviation from the mean value. [d] Mean value of bond angles of the type C(1)-C(2)-C(3).

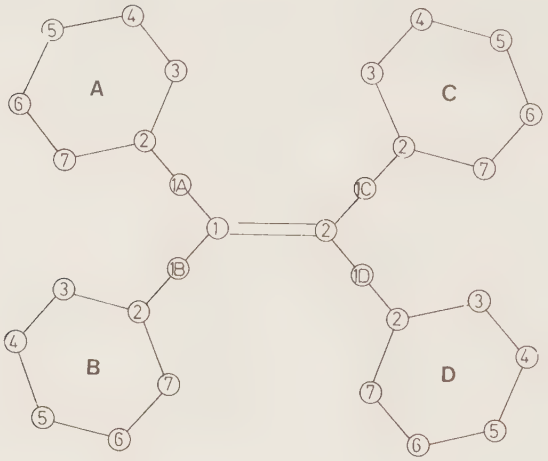
Table V. Calculated Energy Difference Between *syn* and *anti* Conformers of 1,1-, *cis*-1,2-, and *trans*-1,2-dialkylethylenes in kcal/mol

	alkyl group		
subst. pattern	propyl	i-butyl	neopentyl
1,1-	0.43	1.07	0.93
cis-1,2-	0.24	0.36	0.56
trans-1,2-	-0.03	-0.10	-0.15

Table VI. Average Values of Selected Structural Parameters for 5a and 5b

	5a	5b
Bond distances (Å)		
$C_{olef.} - C_{olef.}$	1.324	1.314
$C_{olef.} - CH_2$	1.524	1.505
$CH_2 - C_{Ar}$	1.515	1.518
$C_{Ar} - C_{Ar}$	1.374	1.376
Bond angles (deg)		
$C_{olef.} - C_{olef.} - CH_2$	124.5	124.6
$C_{olef.} - CH_2 - C_{Ar}$	112.7	113.7
$CH_2 - C_{Ar} - C_{Ar}$	121.0	120.8
$C_{Ar} - C_{Ar} - C_{Ar}$	120.0	120.0

Table VII. Selected Dihedral Angles of 5a and 5b



plane 1	plane 2	5a	5b
(1, 1A, 1B)	(2, 1C, 1D)	5.2	4.1
(1, 1A, 2A)	(1, 1A, 1B, 2, 1C, 1D)	76.5	78.0
(1, 1B, 2B)	(1, 1A, 1B, 2, 1C, 1D)	69.3	78.0
(2, 1C, 2C)	(1, 1A, 1B, 2, 1C, 1D)	72.7	74.2
(2, 1D, 2D)	(1, 1A, 1B, 2, 1C, 1D)	61.1	74.2
(1, 1A, 2A)	Ring A	36.5	40.8
(1, 1B, 2B)	Ring B	62.1	40.8
(2, 1C, 2C)	Ring C	60.7	59.5
(2, 1D, 2D)	Ring D	57.7	59.5

Table VIII. Calculated (MMP2) and Experimental Heats of Formation for Selected Cyclophanes

compound	ΔH_f^o (g) (kcal/mol) calcd	expl	ref
2,2-Metacyclophane	39.33	40.7 ±1.9	a
2,2-Metaparacyclophane	42.88	52.18 ± 0.73	a
2,2-Paracyclophane	46.45	57.6 ± 1.0	b
3,3-Paracyclophane	18.01	30.92 ± 0.88	a

a C.-F. Shieh, D. McNally, and R.H. Boyd, Tetrahedron, 1969, 25, 3653.

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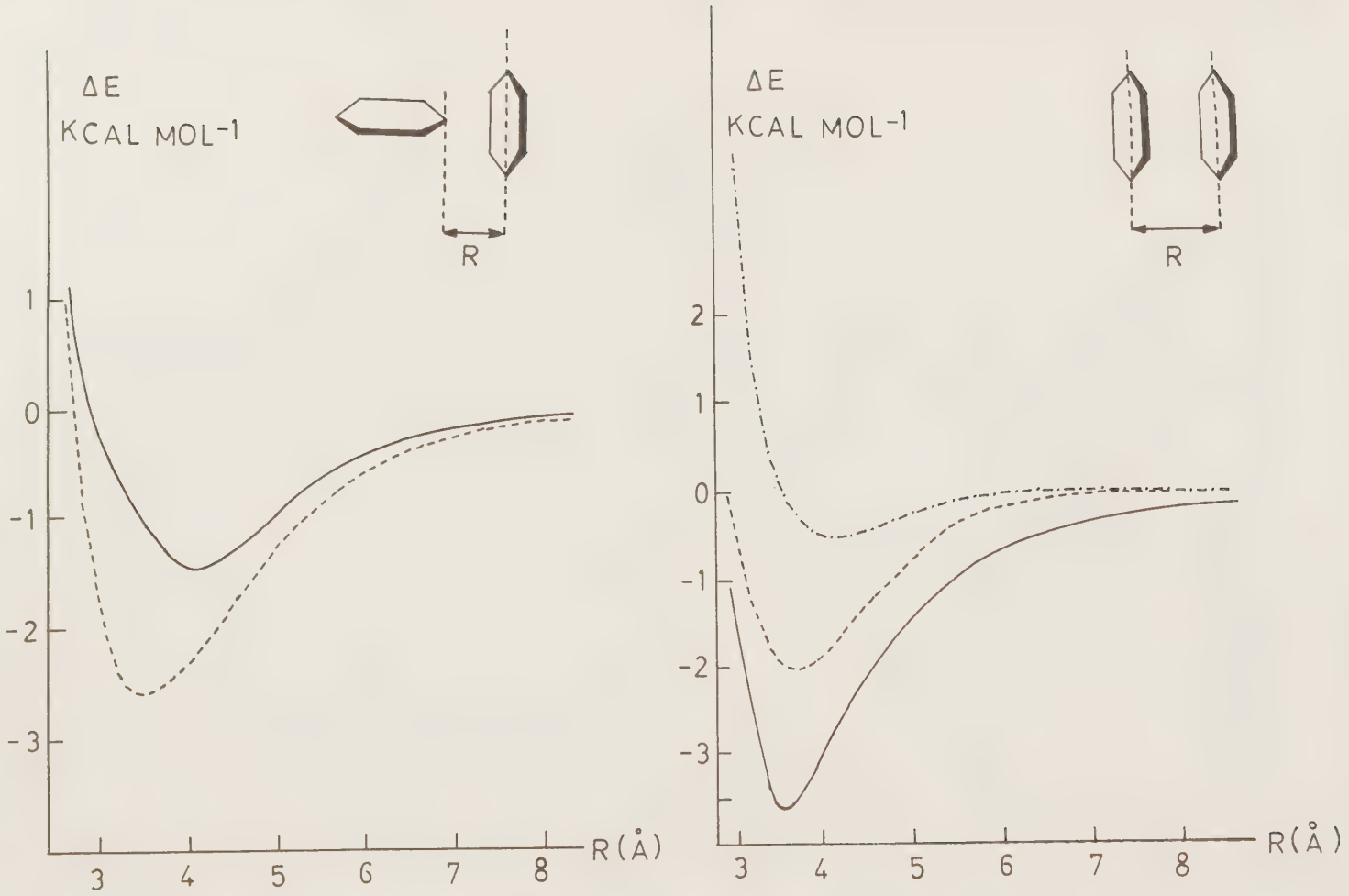

Figure 1. Potential energy curves of the benzene dimer for two different orientations calculated by the MMP2 force field (——), ab initio calculations (-.-.),[14] and from empirical potentials of Evans and Watts (- - -).[15] The latter two curves coincide for the orthogonal arrangment.

Mode

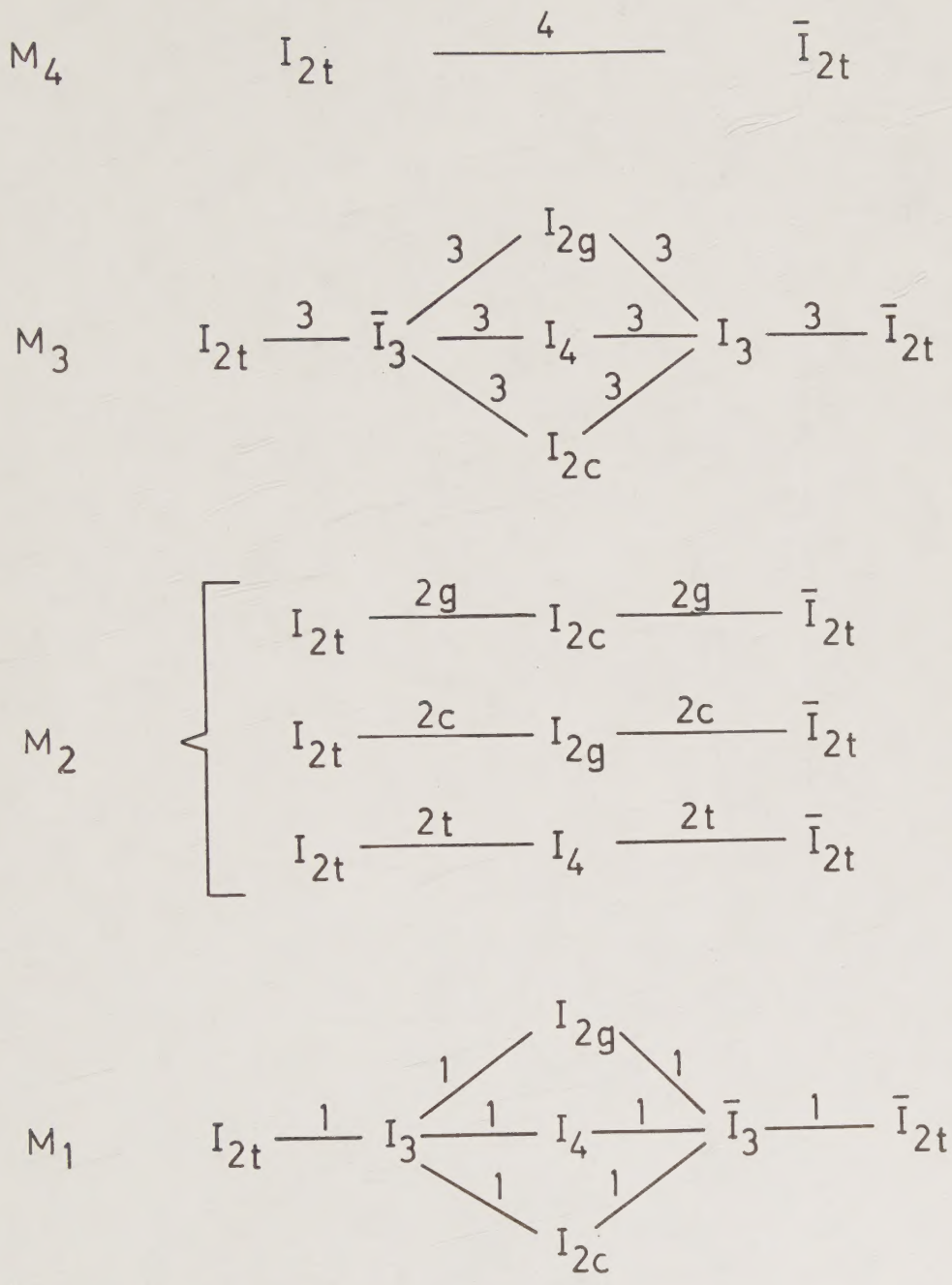

Figure 2. Modes of enantiomerization. Numbers on the lines indicate the number of simultaneously rotating alkyl groups and t, c, and g indicate rotation of trans, cis, and geminal groups, respectively.

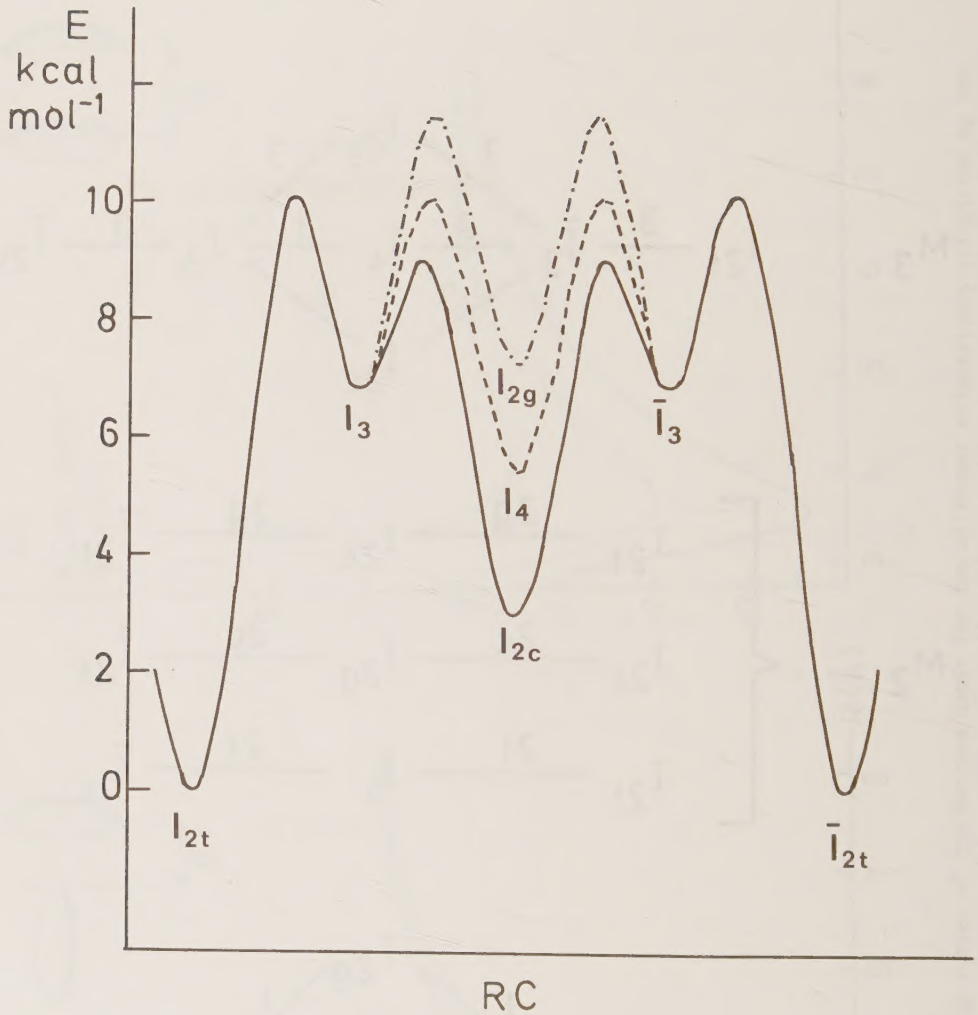

Figure 3. Potential energy curve for enantiomerization of 3 calculated by the MM2 force field. Conformer indices are defined in Table I.

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